AF

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	PICKAR, J., DEY M.
SERIAL NO.	:	09/808,878
FILING DATE	:	March 15, 2001
FOR	:	HORMONE REPLACEMENT THERAPY
EXAMINER	:	Shengjun Wang
GROUP ART UNIT	:	1617

RESPONSE TO NOTIFICATION OF NON-COMPLIANCE WITH THE REQUIREMENTS OF 37 C.F.R. § 41.37(c)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In response to the Notification of Non-Compliance with the Requirements of 37 C.F.R. § 41.37(c), mailed October 14, 2005, Applicants submit herewith a Substitute Appeal Brief complying with the requirements of 37 C.F.R. § 41.37(c). Applicants note that they filed a Request for Oral Hearing on Appeal on April 29, 2004, requesting an oral hearing in connection with this Appeal, and authorizing the Commissioner to charge the required oral hearing request fee and any additional fees to Kenyon & Kenyon deposit account no. 11-0600.

No fee is believed to be due for this submission. If, however, any required fees are due, please charge the required fees to Kenyon & Kenyon deposit account no. 11-0600.

Date: November 14, 2005

Respectfully submitted,

Thomas J. Meloro (Reg. No. 33,538)

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SUBSTITUTE APPEAL BRIEF

Appellants respectfully submit this Substitute Appeal Brief pursuant to 37 C.F.R. § 41.31 in support of their appeal from the final rejection in this application. Appellants note that they filed a Request for Oral Hearing on Appeal on April 29, 2004, requesting an oral hearing in connection with this Appeal.

Real Party in Interest

The real party in interest is the assignee of record, Wyeth.

Related Appeals and Interferences

There are no other appeals or interferences known to the Appellants, or to the Assignee or the Assignee's legal representatives involved in the prosecution of this application that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

Status of Claims

Application serial no. 09/808,878 was originally filed with 68 claims. During prosecution, claims 1-6 and 15-68 were withdrawn in response to a restriction requirement. Claim 69 was added. Subsequently, claims 8-10 and 13-14 were canceled, and claims 7, 11, 12, and 69 were amended. Claims 7, 11, 12, and 69 are pending and stand rejected under 35 U.S.C. §103(a). Appellants appeal the rejection of all pending claims. The appealed claims are reproduced in Appendix A of this brief.

Status of Amendments

No amendments were filed subsequent to final rejection.

Summary of Claimed Subject Matter

Independent claim 7 and dependent claims 11-12 and 69 are pending in this application.

Independent claim 7 recites a method of treating or inhibiting vasomotor symptoms (*See*, specification, ¶ 0026) in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens, USP and a daily dosage of about 1.5 mg of medroxyprogesterone acetate (*See*, specification, ¶ 0011 and original claim 7), wherein the daily dosage of conjugated equine estrogens is between about 0.45 mg and about 0.3 mg (*See*, specification, ¶¶ 0022 and 0026-0028; and original claim 10).

Claim 11 depends from claim 7 and recites that the daily dosage of conjugated equine estrogens, USP is about 0.3 mg (*See*, specification, ¶¶ 0022 and 0026-0028; Figures 1 and 2; and original claim 11).

Claim 12 depends from claim 7 and recites that the vasomotor symptom is hot flushes (*See*, specification, ¶¶ 0026-0028; Figures 1 and 2; and original claim 12).

Claim 69 depends from claim 7 and recites that the daily dosage of conjugated equine estrogens, USP is about 0.45 mg (*See*, specification, ¶¶ 0022 and 0026-0028 and Figures 1 and 2) .

Grounds of Rejection to be Reviewed on Appeal

Claims 7, 11, 12, and 69 are subject to a final rejection under 35 U.S.C. § 103(a) as being unpatentable over U.S. Pat. No. 4,826,831 (Re 36,247) to Plunkett (referred to herein as "Plunkett").

Argument

1. Summary of Argument

In the final Office Action mailed September 10, 2003 (hereinafter "Office Action"), the Examiner rejected claims 7, 11, 12 and 69 of the present application under 35 U.S.C. § 103(a) as being unpatentable over Plunkett. The pending claims of the present application are directed to the continuous and uninterrupted administration of a daily dosage of about 1.5 mg MPA in combination with a dosage between about 0.3 and about 0.45 mg CEE, USP. Plunkett lists a myriad of combinations of various estrogens and progestins in a variety of dosage ranges, in both cyclic and continuous regimens. However, Plunkett does not teach or suggest to one skilled in the art to select the combination of 1.5 mg MPA and about 0.3 to about 0.45 mg CEE for relief of vasomotor symptoms of menopause. Moreover, Plunkett does not describe or suggest a daily dosage of about 1.5 mg MPA at all, much less in combination with the claimed dosage of CEE.

In rejecting the claims under 35 U.S.C. § 103(a), the Examiner bears the initial burden of presenting a *prima facie* case of obviousness. *In re Rijckaert*, 9 F.3d 1531, 1532, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). To establish *prima facie* obviousness, the prior art must teach or suggest all limitations of a claimed invention. See MPEP § 2143.03 and *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Appellants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness because Plunkett does not teach or suggest the selection of about 1.5 mg MPA in combination with about 0.3 to about 0.45 mg CEE for the treatment of vasomotor symptoms. Of the myriad of possibilities within the disclosed genus, Plunkett selects a preferred dose of 2.5 mg of MPA and a preferred dose of 0.600 mg CEE – dosages that are far higher than the 1.5 mg of MPA and the about 0.3 to about 0.45 mg of CEE claimed in the present invention. The evidence of record demonstrates that one skilled in the art would not have been motivated to employ lower dosage with any reasonable expectation of success. The record

evidence also demonstrates that Plunkett does not suggest the specific combination of Appellants' invention.

Furthermore, Appellants have demonstrated that the present invention achieves unexpected results in comparison to the closest prior art. In addition to the data provided in the specification, the Appellants submitted two declarations under 37 C.F.R. § 1.132 by Rogerio A. Lobo, M.D., a Professor of Obstetrics & Gynecology at the Department of Obstetrics and Gynecology at Columbia University, in support of their showing of unexpected results of the claimed invention over Plunkett. (Declaration under 37 C.F.R. §1.132, dated April 1, 2003, attached as Exhibit 1; and Second Declaration under 37 C.F.R. §1.132, dated December 15, 2003, attached as Exhibit 2). The unrefuted declarations of Dr. Lobo establish that the standard daily regimen of 0.625 mg CEE in plus 2.5 mg MPA was considered the minimum effective dosage for relieving vasomotor symptoms. Appellants have demonstrated that the claimed low dose regimen unexpectedly is equally effective at relieving hot flushes. (See Lobo Declaration ¶ 14 and Second Lobo Declaration ¶ 5). Moreover, since the closest species disclosed by Plunkett (0.6 mg CEE plus 2.5 mg MPA) is clinically equivalent to the higher standard dosage, Applicants' demonstration of unexpected results is equally applicable over the Plunkett regimen.

2. Plunkett

Plunkett, the sole reference cited against Appellants' claims, is directed to a broad genus of HRT. In describing estrogen/progestin combination therapy, Plunkett discloses a plethora of estrogens and progestins that can be combined to treat numerous disorders. Specifically, the following *twenty* estrogens are described as being useful in the estrogen plus progestin combination for treating menopausal or post menopausal disorders: estradiol, estradiol-17beta, estradiol valerate, conjugated equine estrogens, estrene, piperazine estrone sulfate, estriol, estriol succinate, polyestriol phosphate, ethinyl estradiol, mestranol, quinestrol, stilbestrol, stilbestrol dipropionate, diethylstilbestrol, chlorotrianiscos, benzoestrol, hexoestrol, and methallenstril. (Plunkett, Table 1A).

Table 1B of Plunkett specifically discloses the following *seventeen* progestins that may be useful in the continuous HRT regimens: levo-norgestrel, dl-norgestrel, norethindrone, norethindrone acetate, dydrogesterone, medroxyprogesterone acetate,

norethynodrel, allylestrenol, lynoestrenol, quingestanol, medrogestone, norgestrienone, dimentisterone, ethisterone, cyproterone acetate, chlormadinone acetate, and magestrol acetate.

Tables 1A and 1B of Plunkett also provide ranges of dosage minimums and maximums, and preferred dosages for the estrogens and progestins listed. For conjugated equine estrogen, Plunkett lists the minimum dosage as 0.3 mg, the maximum dosage as 2.5 mg, and 0.6 mg as the preferred dosage. For medroxyprogesterone acetate, Plunkett provides the minimum dosage as 1 mg, the maximum dosage as 15 mg, and the preferred dosage as 2.5 mg. Plunkett further provides that "[a]ny of the suitable estrogens and progestogens (particularly those listed in the foregoing tables) may be combined with one another in the quantities recited to give estrogen/progestogen combinations within the purview of the invention." (Col. 6, lines 46-50).

Plunkett also provides a list of *twenty* "especially preferred" combinations of estrogen and progestins, only one of which is conjugated equine estrogen with medroxyprogesterone acetate. (col. 6, line 53 - col. 7, line 10). Furthermore, of the thousands of possible combinations of estrogens and progestins, Plunkett only provides data for a single combination in which a study was conducted using a daily regimen of 1 mg 17beta-estradiol plus 75 μg dl-norgestrel. Plunkett does not provide any data for any combinations of conjugated estrogens in combination with medroxyprogesterone acetate.

3. The Claimed Invention is Not Obvious in View of Plunkett

a) The Relevant Legal Standards

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. *See* MPEP §2142. To establish a *prima facie* case of obviousness, the following three criteria must be met: (1) there must be some suggestion or motivation, either in the references or in the knowledge generally available to one skilled in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art must teach or suggest all elements of the claimed invention. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); and *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974). Furthermore, the teaching or suggestion to make the

claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991).

A claim is considered obvious under 35 U.S.C. §103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. 35 U.S.C. §103. The Supreme Court has set forth the following four so-called *Graham* factors to be considered when determining obviousness: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) any secondary indicia of nonobviousness. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1996).

Thus, the obviousness test is not only three elements of primary consideration (scope and content of the prior art, differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art), but also evidence of secondary considerations when such evidence is present. *Simmons Fastener Corp. v. Illinois Tool Works, Inc.*, 739 F.2d 1573, 1575 (Fed. Cir. 1984), *cert. denied*, 471 U.S. 1065 (1985). Secondary considerations include unexpected results, commercial success of the invention, whether the invention solved a long felt need, copying the invention by others in the field, and failure of others to solve the problem that the inventor solved. When unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared to the closest prior art. *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

b) Plunkett Does Not Teach or Suggest Appellants' Claimed Invention

Appellants respectfully submit that the Examiner has not met her burden of establishing a *prima facie* case of obviousness. Plunkett does not teach each and every element of the claimed invention, and does not provide any suggestion or motivation to use the claimed lower dosage amount of CEE and MPA. (*See* Lobo Declaration ¶17-20). Moreover, at the time of the invention, one of ordinary skill in the art would not have had any reasonable expectation of success by using a lower

dosage regimen. As described by Dr. Lobo, the unexpected results showing that a regimen of 1.5 mg MPA in combination with about 0.3 mg to about 0.45 mg CEE reduced the number and severity of hot flushes were contrary to what would have been expected by those skilled in the art. (*See* Lobo Declaration ¶6).

In considering the broad disclosure of Plunkett, one skilled in the art would have to perform undue experimentation to arrive at Appellants' particular low dose combination among the vast possibilities contemplated by Plunkett. Obviousness can only be established if the prior art and/or the knowledge generally available to one of ordinary skill in the art explicitly or implicitly teaches, suggests or motivates those skilled in the art to produce the claimed invention. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1317 (Fed. Cir. 2000). *See also In re Jones*, 958 F.2d 347, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). Appellants respectfully submit that neither Plunkett nor the knowledge generally available to those skilled in the art at the time of the invention suggested or motivated a skilled artisan to use the particular low dose combination claimed by Appellants.

As discussed above, Plunkett discloses a myriad of estrogens and progestins that can be combined to treat numerous disorders. Of the thousands of possibilities with the disclosed genus, Plunkett discloses of 0.600 mg CEE and 2.5 mg of MPA as the preferred doses. (Tables 1A and 1B). Appellants' claims require a dose of about 0.3 to about 0.45 mg CEE and a dose of about 1.5 mg MPA. When the claimed invention is compared with Plunkett's preferred dosage (which is the closest disclosed species), Plunkett's regimen recites a dose of CEE that is between 33% and 100% higher than Appellants' regimen, and a dose of MPA that is 66% higher than Appellants' regimen. Moreover, it is well established that a species is patentable within a prior art genus absent a motivation for one skilled in the art to make the claimed invention. *See, e.g., In re Baird*, 29 U.S.P.Q.2d 1550 (Fed. Cir. 1994); and *In re Jones*, 21 U.S.P.Q.2d 1941 (Fed. Cir. 1992). Nothing in Plunkett, including the closest disclosed species, teaches or suggests the low dose combination claimed by the Appellants.

Furthermore, as described by Dr. Lobo, those skilled in the art considered the commercial regimen of 0.625 mg CEE plus 2.5 mg MPA as the standard dosage of estrogen and MPA necessary to relieve the symptoms of menopause, including hot flushes and bone loss. (Lobo Declaration ¶ 8). Indeed, Dr. Lobo states that the results of the study set forth on page 9 of the specification, showing that the lower doses of CEE and MPA reduced the number and severity of hot flushes, were contrary to what would have been expected by those skilled in the art. (Lobo Declaration ¶ 6). Accordingly, the teachings of the prior art and the knowledge generally available in the art would not have suggested to those skilled in the art that the use of 1.5 mg MPA in combination with about 0.3 mg to about 0.45 mg CEE would have been reasonably successful in providing relief of vasomotor symptoms of menopause.

Moreover, even assuming *arguendo* that it would have been *obvious to try* Appellants' low dose combination, as the Examiner has suggested, this is not the appropriate standard to use in reaching an obviousness determination. *See In re Fine*, 837 F.2d 1071, 1075-76, 5 U.S.P.Q.2d at 1598-1600 (Fed. Cir. 1988). The Federal Circuit in *In re Fine* stated that:

> The PTO has the burden under section 103 to establish a prima facie case of obviousness. It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. This it has not done . . . .
>
> * * *
>
> Instead, the Examiner relies on hindsight in reaching his obviousness determination . . . . One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

Id.

It is respectfully submitted that the Examiner offers no evidence, but only conclusory, hindsight speculation in support of her position of obviousness. However, when applying 35 U.S.C. §103, the prior art reference must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. *See Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986); and MPEP §2141. In this instance, the unrefuted evidence provided by the Appellants shows that optimization of the dosage

amounts was not obvious to one of skill in the art because the selected Plunkett regimen was accepted as the minimum dosage necessary to provide relief from hot flushes. (*See* Lobo Declaration ¶ 8).

c) Appellants Have Demonstrated Unexpected Results Over the Closest Prior Art

The Appellants respectfully submit that even assuming *arguendo* that the Examiner had established a *prima facie* case of obviousness, the evidence provided by the Appellants clearly rebuts the *prima facie* case by showing that the claimed invention possesses unexpectedly improved properties. The Appellants have provided data demonstrating unexpected results over the closest prior art. Evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. *See In re Boesch*, 617 F.2d 272, 205 U.S.P.Q. 215 (C.C.P.A. 1980). *See also* MPEP §716.02(d)-§716.02(e).

The pending application provides data setting forth some of the results of a double blind clinical study of postmenopausal women using combinations of PREMARIN (conjugated estrogens tablets, USP) plus MPA, or placebo. (*See* Pages 8-9). The results of the study reported on page 9 of the specification surprisingly and unexpectedly demonstrated that providing a much lower daily dosage of 1.5 mg MPA in combination with 0.45 or 0.30 mg CEE reduced the number and severity of hot flushes to essentially the same extent as the standard, commercially available dose combination of 0.625 mg CEE and 2.5 mg MPA. (Second Lobo Declaration ¶6).

As explained by Dr. Lobo, for the past 20 years, the dosage of 0.625 mg CEE has been accepted as the minimum dosage of estrogen necessary to relieve the symptoms of menopause, including vasomotor symptoms. Furthermore, the dosage of 2.5 mg of MPA has been recognized as the minimum amount needed to oppose 0.625 mg CEE and to protect the endometrium. This daily dosage combination of 0.625 mg CEE plus 2.5 mg MPA has been the most commonly prescribed combination estrogen-progestin hormone replacement therapy regimen in the United States. (*See* Second Lobo Declaration ¶ 2).

The closest species disclosed by Plunkett, which is 0.600 mg CEE plus 2.5 mg MPA, is equivalent to the commonly prescribed higher dosage regimen, 0.625 mg

CEE plus 2.5 mg MPA. Although there is a slight variation in the dosage of CEE, one skilled in the art would consider a daily dosage of 0.625 mg CEE to be clinically equivalent to a dosage of 0.600 mg CEE for the purposes of treating vasomotor symptoms. (*See* Second Lobo Declaration ¶ 3). Because the commonly prescribed regimen (0.625 mg CEE in combination with 2.5 mg MPA) and the closest species disclosed in Plunkett are equivalent, Appellant's demonstration of unexpected results over the commonly prescribed regimen is equally applicable to show unexpected results over the Plunkett regimen.

As set forth in Dr. Lobo's first declaration, he worked with other scientists and doctors to develop the clinical protocol for the study reported on page 9 of the specification, referred to as the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study"), and was involved as a trial investigator. (Lobo Declaration ¶ 9). In the H.O.P.E. study, patients received continuous and uninterrupted treatment for 13 to 26 cycles, consisting of the following eight regimens administered daily: (1) 0.625 mg CEE; (2) 0.45 mg CEE; (3) 0.3 mg CEE; (4) 0.625 mg CEE plus 2.5 mg MPA ("PREMPRO"); (5) 0.45 mg CEE plus 2.5 mg MPA; (6) 0.45 mg CEE plus 1.5 mg MPA; (7) 0.3 mg CEE plus 1.5 mg MPA; and (8) a placebo. (Lobo Declaration ¶ 11).

The results from the H.O.P.E. study surprisingly and unexpectedly demonstrated that all doses of CEE and MPA reduced the number and severity of hot flushes experienced by the women in this study compared with women taking placebo. (Lobo Declaration ¶ 14). Specifically, it was unexpected that providing a daily dosage of 1.5 mg MPA in combination with the lower doses, 0.45 or 0.30 mg, CEE, rapidly reduced the number and severity of hot flushes to the same extent as the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA. (Lobo Declaration ¶ 14).

Moreover, the H.O.P.E. study further unexpectedly showed an additive effect of MPA at low doses. Prior studies using various dosages of CEE had demonstrated that MPA had no additive effect in relieving vasomotor symptoms, and the presence of MPA was thought to be merely prophylactic (Lobo Declaration ¶ 15). That is, it was thought that CEE plus MPA was no more effective in relieving hot flushes as compared to CEE alone. However, the H.O.P.E. study surprisingly demonstrated that the particular low dose of 1.5 mg MPA may contribute vasomotor relief in

combination with the lower dosages of 0.3 or 0.45 mg CEE. Thus, Appellants' invention unexpectedly contradicts the accepted view by demonstrating the additive effect of MPA at low dosages.

The Appellants respectfully disagree with the Examiner's position that the data provided on page 9 of the specification does not constitute unexpected results because the data presented shows similar efficacy in treating vasomotor symptoms between the standard commercially available regimen, 0.625 mg CEE/2.5 mg MPA, and the lower dosage regimens claimed herein, 0.45 mg CEE/1.5 mg MPA and 0.30 mg CEE/1.5 mg MPA. (Office Action, p. 4). The Examiner further noted that some of the data points overlap in both number and severity of hot flushes. However, these similar therapeutic results that are reported on page 9 of the specification are precisely what was unexpected to one skilled in the art.

As explained in Dr. Lobo's declarations, prior to the Appellants' invention, one skilled in the art would expect that a low dose regimen would have *some effect* in reducing the number and severity of hot flushes. However, a skilled artisan would have expected *far less of an effect* than the standard dose of 0.625 mg CEE plus 2.5 mg MPA. (Lobo Declaration ¶ 12 and Second Lobo Declaration ¶ 6). In fact, Dr. Lobo and others skilled in the art doubted that a study of low dose regimens was worth the economic effort. (Lobo Declaration ¶ 12). Despite the presumption that the standard regimen was the minimum effective dose, Appellants demonstrated that the low dose regimen was *equally effective* at relieving hot flushes. (Lobo Declaration ¶ 14 and Second Lobo Declaration ¶ 5).

Appellants also respectfully disagree with the Examiner's assertions that because the lower dosage combinations yielded similar therapeutic results as with the standard commercially available combination, the Appellants have confirmed the teachings of Plunkett that the entire range is effective in treating hot flushes. Appellants are required to compare their claimed invention with the closest species disclosed in the prior art. *See* MPEP §2144.08(II)(A)(2) ("the closest disclosed species or subgenus in the prior art reference should be identified and compared to that claimed."). In Plunkett, the closest species is 0.600 mg CEE in combination with 1.5 mg MPA. Applicants have made such a comparison and have demonstrated unexpected results over Plunkett. Appellants respectfully submit that contrary to the

Examiner's position, they do not confirm the efficacy of the entire Plunkett genus, but rather only demonstrate the efficacy of the claimed low dose regimen.

The Examiner states that Dr. Lobo's declaration does not clearly and convincingly show unexpected benefits residing in the claimed dosage regimen. Appellants respectfully disagree. Dr. Lobo's statements are not only based on cited references, but are also based on his knowledge as a practicing physician in the field. Dr. Lobo has extensive experience in treating women for symptoms of menopause, including hot flushes, and has knowledge of what other skilled in the art prescribed for their patients. Thus, the evidence provided by Dr. Lobo should be given a great deal of weight in the determination of patentability of the pending claims.

Conclusion of Argument

It is respectfully submitted that the Examiner has not made a *prima facie* case of obviousness because Plunkett, the sole reference cited against the Appellants' claims, does not teach or suggest the selection of about 1.5 mg MPA in combination with about 0.3 to about 0.45 mg CEE, as recited in the appealed claims. Furthermore, the unrefuted evidence provided in the specification and by Dr. Lobo convincingly demonstrates the unexpected results obtained with Appellants' invention. Accordingly, Appellants respectfully submit that the rejection of the appealed claims should be reversed.

Fee Authorization

In the original appeal brief, filed October 19, 2004, the Commissioner was authorized to charge the fee for the Appeal Brief and any other fees necessary for the consideration of this appeal. No additional fees are believed to be due for submission of this Substitute Appeal Brief. If, however, any required fees are due, please charge the required fees to Kenyon & Kenyon Deposit Account No. 11-0600.

Respectfully submitted,

Dated: November 14, 2005

Thomas J. Meloro
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Claims Appendix

7. A method of treating or inhibiting vasomotor symptoms in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens, USP and a daily dosage of about 1.5 mg of medroxyprogesterone acetate, wherein the daily dosage of conjugated equine estrogens is between about 0.45 mg and about 0.3 mg.

11. The method according to claim 7, wherein the daily dosage of conjugated equine estrogens, USP is about 0.3 mg.

12. The method according to claim 7, wherein the vasomotor symptom is hot flushes.

69. The method according to claim 7, wherein the daily dosage of conjugated equine estrogens, USP is about 0.45 mg.

Evidence Appendix

The Declaration Under 37 C.F.R § 1.132 of Dr. R. Lobo and the Second Declaration Under 37 C.F.R § 1.132 of Dr. R. Lobo, set forth below as tab 1 and tab 2, respectively, were filed as an attachment to the April 1, 2003 Response to Office Action and the January 9, 2004 Response to Office Action, respectively.

Related Proceedings Appendix

There are no other appeals or interferences known to the Appellants, or to the Assignee or the Assignee's legal representatives involved in the prosecution of this application that will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

[AM100226]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S)	:	PICKAR, J., DEY M.
SERIAL NO.	:	09/808,878
FILED	:	March 15, 2001
TITLE	:	HORMONE REPLACEMENT THERAPY
ART UNIT	:	1617
EXAMINER	:	M. Bahar

Assistant Commissioner
for Patents
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. § 1.132

SIR:

I, ROGERIO A. LOBO, M.D., declare as follows:

1. I am currently a Professor of Obstetrics & Gynecology at the Department of Obstetrics and Gynecology, Columbia University in New York, New York, and I served as Rappleye Professor and Chairman of the Department of Obstetrics and Gynecology from 1995 until July 2002. I received a medical degree from Georgetown University Medical School in 1974. I completed an internship from 1974 to 1975 and a residency from 1975 to 1978 at the University of Chicago, Department of Obstetrics & Gynecology. I was a Clinical Research Fellow at the University of Southern California Medical Center in Los Angeles, California from 1978 to 1980.

2. From 1978 until 1995, I held a number of academic medical positions at the University of Southern California, Los Angeles, California. From 1978 to 1980, I was a Clinical Instructor, Division of Reproductive Endocrinology and Infertility, Department of

Obstetrics and Gynecology. I was an Assistant Professor, Department of Obstetrics & Gynecology from 1980 to 1984, an Associate Professor from 1984 to 1988, and a Professor from 1988 to 1995. From 1984 to 1995, I was Chief and Director of the Division of Reproductive Endocrinology and Infertility.

3. In the past twenty-three years, I have been an author or co-author of at least 313 papers published in peer-reviewed journals, 99 book chapters and 314 abstracts, and have been an editor of 25 books. Many of these publications are in the area of the menopause and treatments of the symptoms of menopause including hormone replacement therapy. (See, e.g., Rogerio A. Lobo, ed., Treatment of the Postmenopausal Woman: Basic and Clinical Aspects (2d ed., Philadelphia, PA: Lippincott Williams & Wilkins 1999)).

4. I am a member of a number of professional societies, including the International Menopause Society and the North American Menopause Society. I have served as a consultant to and have served on the editorial board of numerous medical journal specializing in obstetrics and gynecology, including *Obstetrics and Gynecology*, *The Journal of Reproductive Medicine* and *Fertility and Sterility*. Additional acts about my background and qualifications including a list of my publications are set forth in my curriculum vitae, attached as Exhibit A.

5. My private practice consists of gynecology with a focus on the treatment of premenopausal, menopausal and postmenopausal women. I have also participated in a number of clinical studies evaluating various treatments, including hormone replacement therapy, for the symptoms of menopause including hot flushes and decreased bone density.

6. By way of background, menopause generally refers to the cessation of the menses and ovarian function. In other words, the ovaries no longer produce estrogen. Approximately one-third of a woman's life is spent in the estrogen-deficient postmenopausal

state. Symptoms of estrogen deficiency include hot flushes, vaginal atrophy, depression, decrease in bone mass and changes in blood lipid levels, which may be precursors to cardiovascular diseases. Conjugated equine estrogens ("CEE") have been prescribed for over 50 years to treat these symptoms. However, for a woman with an intact uterus, estrogen therapy has been shown to increase the risk of endometrial hyperplasia (abnormalities in the cells that are a precursor to endometrial carcinoma) and endometrial carcinoma (endometrial cancer). The risk is substantially reduced when a progestin is administered concurrently.

7. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial demonstrated that estrogen-progestin combinations protect against endometrial hyperplasia. (See The Writing Group for the PEPI Trial, "Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial," JAMA 275(5):370-5 (1996)). The PEPI trial involved 596 healthy postmenopausal women aged 45 to 74 years at seven clinical centers in the U.S. from 1987 to 1993. The women were randomly assigned to one of five treatment groups: (1) a placebo; (2) 0.625 mg CEE daily; (3) 0.625 mg CEE daily plus 10 mg of a progestin, medroxyprogesterone acetate ("MPA") for 12 days per month; (4) 0.625 mg CEE daily plus 2.5 mg MPA daily[1]; or (5) 0.625 mg of estrogen daily plus 200 mg of a natural (micronized) progesterone for 12 days per month. A large proportion of women with a uterus who received unopposed 0.625 mg CEE developed endometrial hyperplasia. However, the addition of a progestin, 2.5 mg MPA, to the 0.625 mg CEE provided protection of the endometrium.

8. For the past 20 years, 0.625 mg CEE has been accepted as the standard dosage of estrogen necessary to relieve the symptoms of menopause, including hot flushes

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[1] This is the regimen used in PREMPRO, Wyeth's commercially-marketed combination low dose hormone replace therapy.

and bone loss. (See, e.g., Lindsay et al., Obstetrics and Gynecology, 63:759-763 (1984)). The dosage of 2.5 mg of MPA has been recognized as the minimum amount needed to oppose 0.625 mg CEE and protect the endometrium. This combination of 0.625 mg CEE plus 2.5 mg MPA daily has been the most commonly prescribed hormone replacement therapy regimen in the United States. (See Archer et al., Fertility and Sterility, 75:1080-1087 (2001)).

9. A double blind clinical study of postmenopausal women was conducted using combinations of conjugated equine estrogens ("CEE") and the progestin, medroxyprogesterone acetate ("MPA"). Patients received continuous and uninterrupted treatment for 13 or 26 cycles. This study is referred to as the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study"). The study was conducted at 57 centers across the United States and included 2,673 healthy postmenopausal women aged 40 to 65. I worked with other scientists and doctors to develop the clinical protocol for the H.O.P.E. study and was involved as a trial investigator.

10. The objectives of the H.O.P.E. study were to evaluate the safety and efficacy of lower doses of Premarin and MPA in reducing the incidence of endometrial hyperplasia, relieving menopausal symptoms and maintaining an acceptable metabolic profile. Another sub-part of the study focused on bone mineral density and was conducted over a 26 cycle period.

11. The doses used in the H.O.P.E. study consisted of eight regimens administered daily: (1) 0.625 mg CEE; (2) 0.45 mg CEE; (3) 0.3 mg CEE; (4) 0.625 mg CEE plus 2.5 mg MPA ("PREMPRO"); (5) 0.45 mg CEE plus 2.5 mg MPA; (6) 0.45 mg CEE plus 1.5 mg MPA; (7) 0.3 mg CEE plus 1.5 mg MPA; and (8) a placebo.

12. It was conventional wisdom that the dose of 0.625 mg CEE was the minimum effective dose to relieve vasomotor symptoms ("hot flushes"). I and others

expected that the study would show that there would be a dose response such that the lower combination doses of CEE and MPA would have some effect in reducing the number and severity of hot flushes compared with the placebo, but far less of an effect than the standard dose of CEE 0.625 plus 2.5 mg MPA. In fact, I and others were interested in seeing the results of the various lower doses, but doubted the study was worth the economic effort.

13. Relief of vasomotor symptoms was analyzed in patients who experienced at least an average of 7 to 8 moderate-to-severe hot flushes per day during the 7-day period just prior to the initiation of treatment in this study.

14. It was very surprising and unexpected that the data from the H.O.P.E. study demonstrated that all doses of CEE and MPA reduced the number and severity of hot flushes experienced by the women in this study compared with women taking placebo. It was unexpected that providing a daily dosage of 1.5 mg MPA in combination with the lower doses, 0.45 or 0.30 mg, CEE, rapidly reduced the number and severity of hot flushes to the same extent as the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

15. Moreover, at these particular low doses of 1.5 mg MPA, an additive effect of vasomotor symptom relief is seen. The H.O.P.E. study demonstrated that dosages of CEE and MPA may be better than equivalent dosages of unopposed CEE for vasomotor symptom relief. Previous studies with various dosages of CEE showed no additive effect of MPA on vasomotor relief. (See Greendale et al., Obstetrics and Gynecology, 92:982-988 (1998)). Instead, the presence of MPA was thought to be merely prophylactic (to prevent endometrial cancer). The H.O.P.E. study surprisingly demonstrated that at these low doses MPA may contribute to ameliorating the vasomotor symptoms.

16. Prior to the H.O.P.E. study, the dosage of MPA necessary to provide endometrial protection with lower dosages of CEE was unknown. We entered unchartered waters in conducting the H.O.P.E. study as to the endometrial risk posed by the lower daily dosage combinations of 0.45 or 0.3 mg CEE and 1.5 mg MPA. The endometrial biopsies[2] evaluated as part of the H.O.P.E. study demonstrated that providing a daily dosage of 1.5 mg MPA effectively inhibited the development of endometrial hyperplasia when opposing the lower doses, 0.45 or 0.30 mg, CEE. These biopsy results were not statistically different from the higher dose hormone replacement therapy combination containing 2.5 mg MPA.

17. The prior art Plunkett patent cited by the examiner is directed to combinations of various estrogens and progestins. Plunkett lists a myriad of such combinations over a variety of dosage ranges, in both cyclic and continuous regimes. There is nothing in the Plunkett patent that teaches one skilled in the art to select the combination of 1.5 mg MPA and about 0.3 to about 0.45 mg CEE for relief of vasomotor symptoms of menopause from the thousands of possible estrogen-progestin combinations.

18. The preferred dosages of MPA and CEE that Plunkett discloses are 2.5 mg MPA and 0.600 mg CEE. These dosages are much higher than the dosages claimed in the present invention -- 1.5 mg MPA and about 0.3 to about 0.45 mg CEE.

19. Plunkett does not teach the importance of balancing the dosages of MPA and CEE, particularly at very low doses. Specifically, Plunkett does not teach that the selection of 1.5 mg MPA would provide relief of vasomotor symptoms achieved in combination with about 0.3 to about 0.45 mg CEE

20. Further, Plunkett does not teach that an additive vasomotor effect is exhibited by the low dose of MPA to the lower doses of CEE (0.3 to about 0.45 mg CEE).

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[2] An endometrial biopsy is a cell sample of the endometrium taken to evaluate whether any abnormal cells exist.

21. In conclusion, the results of the H.O.P.E. study unexpectedly demonstrated that the combinations of a daily dosage of 1.5 mg MPA with 0.3 or 0.45 mg CEE are effective in treating vasomotor symptoms. In my opinion, these dosage combinations would not have been obvious at the time of the invention to relieve vasomotor symptoms.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent or any reexamination certificate issued therefor.

Dated: 4/1/03

ROGERIO A. LOBO, M.D.

Updated: 3/24/03

Curriculum Vitae

ROGERIO A. LOBO, M.D.

Date of birth:	October 26, 1949
Place of birth:	Hong Kong
Citizenship:	Naturalized United States Citizen
Marital Status:	Married (Jessie C. Lobo)
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Licensure and Certifications:	State of California Medical License No. G-36128
	The University of the State of New York Medical License No. 198859
	DEA No. AL822046
	Diplomate, National Board of Medical Examiners, 1975
	Diplomate, The American Board of Obstetrics and Gynecology, Inc. 1981
	Diplomate, The American Board of Obstetrics and Gynecology, Inc. Division of Reproductive Endocrinology, 1982
	Recertified Diplomate, The American Board of Obstetrics and Gynecology Inc. 1994

Education:

1967-1995

Georgetown University
Washington, D.C.

B.Sc. (Cum Laude)
Major: Biology

1970- 1974

Georgetown University Medical School
Washington, D.C.
M.D.

Postgraduate Training:

1974- 1975

Intern
Department of Obstetrics & Gynecology
The Chicago Lying-In-Hospital
The University of Chicago
Chicago, Illinois

1975- 1978

Resident
Department of Obstetrics and Gynecology
The Chicago Lying-In-Hospital
The University of Chicago
Chicago, Illinois

1978-1980

Clinical Research Fellow
Division of Reproductive Endocrinology and Infertility

Department of Obstetrics and Gynecology
Los Angeles County/University of Southern California Medical Center
Los Angeles, California

Academic Positions:

1978-1980

Clinical Instructor
Division of Reproductive Endocrinology and Infertility
Department of Obstetrics and Gynecology
University of Southern California
Los Angeles, California

1980-1984

Assistant Professor
Department of Obstetrics and Gynecology
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1984-1988

Associate Professor
Department of Obstetrics & Gynecology
University of Southern California
Los Angeles, California

1988- 1985	Professor Department of Obstetrics & Gynecology University of Southern California Los Angeles, California
1984- 1995	Chief, Division of Reproductive Endocrinology and Infertility Department of Obstetrics and Gynecology Los Angeles County/University of Southern California Medical Center Los Angeles, California
1984-1995	Director, Reproductive Endocrinology and Infertility Training Program Fellows and students directed in training are underlined under list of publications
1995-2002	Rappleye Professor and Chairman Department of Obstetrics and Gynecology Columbia University College of Physicians and Surgeons New York, New York
7/1/02-present	Professor of Obstetrics & Gynecology Department of Obstetrics and Gynecology Columbia University College of Physicians and Surgeons New York, New York

Other Hospital Affiliations:

1980- 1995	Consultant City of Hope National Medical Center Duarte, California
1984-1995	California Medical Center Los Angeles, California
1986-1991	Director University of Southern California/ California Hospital Reproductive Health Institute Los Angeles, California
1991- 1995	USC University Hospital Los Angeles, California

Outside Consultantships:

Abbott Diagnostics
North Chicago, Illinois

Medical Advisory Board
Mead Johnson Laboratories
Princeton, New Jersey

Progynon Associates
Rosemont, Illinois

Division of Endocrinology and Metabolism
Robert Wood Johnson Pharmaceutical Research Institute
New Brunswick, New Jersey

Advisory Board on Hormone Replacement Therapy
Schering Laboratories
Kenilworth, New Jersey

Reproductive Endocrinology Luminary Program
Serono Laboratories
Norwell, Massachusetts

Advisory Board
TAP Pharmaceuticals, Inc.
Deerfield, Illinois

Wyeth-Ayerst Research
Philadelphia, Pennsylvania

Board of Trustees
The Berlex Foundation
Dumont, New Jersey

Advisory Boards:
- Solvay
- Ortho
- Lilly
- Merck

Membership in Professional Societies:

International Menopause Society
Pacific Coast Fertility Society
Society for Gynecologic Investigation
The American College of Obstetricians and Gynecologists
American Society for Reproductive Medicine
The American Gynecological and Obstetrical Society
The Endocrine Society
The North American Menopause Society

Membership in Committees:

The Society of Reproductive Endocrinologists

1983- 1984	Medical Education Committee III-year students
1984-1985	Grand Rounds Program Coordinator Department of Obstetrics and Gynecology Los Angeles County/University of Southern California Medical Center Los Angeles, California
1984- 1987	Board of Directors Pacific Coast Fertility Society Los Angeles, California
1984	Awards Committee Pacific Coast Fertility Society Los Angeles, California
1984	Special Study Section National Institutes of Health Bethesda, Maryland
1984- 1995	Executive Committee Department of Obstetrics and Gynecology Los Angeles County/University of Southern California Medical Center, Los Angeles, California
1985- 1986	Search Committee for Dean University of Southern California School of Medicine Los Angeles, California
1985- 1995	Admissions Committee for Students University of Southern California School of Medicine Los Angeles, California
1986	External Referee Medical Research Council of Canada Ottawa, Canada
1986- 1995	Advisory Committee on Policy American Journal of Obstetrics & Gynecology
1987	Program Chairman Pacific Coast Fertility Society Los Angeles, California

1987- 1995	Ad Hoc Committee for Promotions University of Southern California School of Medicine Los Angeles, California
1987- present	Examiner Basic Obstetrics and Gynecology and Reproductive Endocrinology Oral Examinations The American Board of Obstetrics and Gynecology, Inc. Seattle, Washington
1988	Steering Committee National Cholesterol Education Program National Heart, Lung and Blood Institute National Institutes of Health Bethesda, Maryland
1988	Program Chairman Society for Gynecologic Investigation Washington, D.C.
1988	Chairman Poster Prize Presentation Committee The American Fertility Society Birmingham, Alabama
1988-1995	Chairman, Institutional Review Committee California Medical Center Los Angeles, California
1988-1995	Advisory Committee General Clinical Research Center University of Southern California School of Medicine Los Angeles, California
1988-1992	Reproductive Endocrinology Study Section Division of Research Grants National Institutes of Health Bethesda, Maryland
1989- 1995	Secretary-Treasurer Society for Gynecologic Investigation Washington, D.C.
1989	Exhibits Chairman Pacific Coast Fertility Society

	Los Angeles, California
1991- 1992	Vice President Pacific Coast Fertility Society La Mirada, California
1992- 1993	President Pacific Coast Fertility Society La Mirada, California
1992- 1996	Reviewers Reserve National Institutes of Health Bethesda, Maryland
1992- 1993	Program Chairman The North American Menopause Society Cleveland, Ohio
1993- 1996	Board of Directors The American Fertility Society Birmingham, Alabama
1995-	American Board of Obstetrics & Gynecology Division of Reproductive Endocrinology
1997-1998	President, Society for Gynecologic Investigation

Committees at Columbia University College of Physicians and Surgeons:

CPPN Board
Executive Committee, Medical Board
Surgical Directors Committee
Clinical Chairs Committee
Directors of Service Committee
Dean's Committee on Hospital Appointments

Consultant for the Following Journals:

Acta Endocrinologica
American Journal of Medicine
American Journal of Nephrology
Archives of Internal Medicine
Clinical Chemistry
Contraception
Endocrinology
Epidemiology
European Journal of Obstetrics,
Gynecology and Reproductive Biology
Fertility and Sterility
Gynecologic Oncology
Gynecological Endocrinology
International Journal of Gynaecology and Obstetrics

Journal of Endocrinological Investigation
Journal of the American Medical Association
Life Sciences
New England Journal of Medicine
Obstetrics and Gynecology
The Journal of Clinical Endocrinology
and Metabolism
The Journal of Reproductive Medicine
Journal of In Vitro Fertilization and Embryo Transfer
Proceedings of the National Academy of Science
Australian Medical Journal

Editorship:

Editor-in-Chief
Journal of Society for Gynecological Investigation

Journal Editorships/Editorial Board:

Clinical Pathological Conferences in
Obstetrics and Gynecology

Clinics in Endocrinology and Metabolism

Fertility and Sterility
(Editorial Board, 1986-1993)

Gynecological Endocrinology
(Editorial Board)

Journal of the Society for Gynecologic
Investigation

Menopause Management
(Editorial Board)
Seminars in Reproductive Endocrinology

The American Journal of Obstetrics and
Gynecology, Society for Gynecologic
Investigation issue (1986-1993)

The Journal of Maternal-Fetal Medicine
(Editorial Board)

The Journal of Reproductive Medicine
(Editorial Board)

The Journal of Clinical Endocrinology & Metabolism
(Editorial Board) (1/1/97-12/31/2000)

(Editorial Board) 8/1/2000-

Lectureships:

Multiple visiting professorships and speaking engagements. Postgraduate courses and other teaching assignments (medical students, residents, etc) not specifically listed.

Honors and Awards:

Serono Award (In-Training) Paper entitled: The Role of DHEA-S in the Evaluation of Hirsute Women. Presented at the 27th Annual Meeting of the Pacific Coast Fertility Society, October 17-21, 1979, Rancho Mirage, California.

Serono Award (In-Training). Paper entitled: Elevations in Unbound Serum Estradiol as a Possible Mechanism for Inappropriate Gonadotropin Secretion in Women with PCO Presented at the 28th Annual Meeting of the Pacific Coast Fertility Society, October 15-19, 1980, Scottsdale, Arizona.

Wyeth Award. Paper entitled: The Relationship Between Psychological Stress, Neurotransmitters and Androgen Secretion in Women With PCO. Presented at the 29th Annual Meeting of the Pacific Coast Fertility Society October 14-18, 1981, Rancho Mirage, California

Squibb Award. Paper entitled: Hirsutism in Polycystic Ovary Syndrome (PCO). Presented at the 30th Annual Meeting of the Pacific Coast Fertility Society, October 13-17, 1982, Scottsdale, Arizona

Squibb Award
Paper entitled: The Effects of Spironolactone on Adrenal Steroidogenesis in Hirsute Women
Presented at the 32nd Annual Meeting of the Pacific Coast Fertility Society
September 19-23, 1984,Rancho Mirage, California

Wyeth Award
Paper entitled: Prolactin (PRL) Modulates Peripheral Androgen Metabolism (PAM)
Presented at the 33rd Annual Meeting of the

Pacific Coast Fertility Society
April 24-28, 1985
Las Vegas, Nevada

Wyeth Award
Paper entitled: Acute Modulation of the
Hypothalamic-Pituitary Axis (HPA) by
Testosterone (T) in Normal Women
Presented at the 32nd Annual Meeting of the Society for
Gynecologic Investigation
March 20-23, 1985
Phoenix, Arizona

Lester T. Hibbard Award
Outstanding Faculty, 1985
Department of Obstetrics and Gynecology
Los Angeles County/University of Southern
California Medical Center
Los Angeles, California

Second Prize
Paper entitled: Genital Skin 5_{α}Reductase
Activity (5_{α}RA): A Marker of Androgenicity
in Women
Presented at the 4th Annual Meeting of
The American Gynecological and Obstetrical Society
September 4-7, 1985
Hot Springs, Virginia

Squibb Award
Paper entitled: Clinical Heterogeneity in
Turner's Syndrome
Presented at the 34th Annual Meeting of the
Pacific Coast Fertility Society
April 9-13, 1986
San Diego, California

Special Prize Forum
Paper entitled: Differential Pathways of 3_{α}
Androstanediol Glucuronide (3_{α}diol G)
Formation in Human Skin
Presented at the 34th Annual Meeting of the
Society for Gynecologic Investigation
March 18-21, 1987, Atlanta, Georgia

Special Prize Forum
Paper entitled: Opiates Modulate the
Inhibitory Effects of Androgen on the
Hypothalamic-Pituitary Axis (HPA) of Normal Women
Presented at the 34th Annual Meeting of the
Society for Gynecologic Investigation
March 18-21, 1987, Atlanta, Georgia

Serono Award (1st Prize)
Paper entitled: Adrenal Effects of Short-Term
Administration of Testosterone in Normal Women
Presented at the 35th Annual Meeting of the
Pacific Coast Fertility Society
May 6-10, 1987, Palm Springs, California

Serono Award (2nd Prize)
Paper entitled: Secretory Dynamics of
Bioactive and Immunoreactive PRL in PCO
Presented at the 35th Annual Meeting of the
Pacific Coast Fertility Society, May 6-10, 1987
Palm Springs, California

Outstanding Teacher Award, 1988
Department of Family Medicine
University of Southern California
School of Medicine, Los Angeles, California

Serono Award (2nd Prize). Paper entitled: Decreased Responses of ACTH to Ovine Corticotropin-Releasing Factor (OCRF) and Increased Adrenal Insensitivity in Hyperandrogenic Women
Presented at the 37th Annual Meeting of the
Pacific Coast Fertility Society
April 12-16, 1989, Palm Springs, California

Wyeth Award
Paper entitled: Human Chorionic Gonadotropin (hCG)
Enhances Progestin Stimulation of Prolactin (PRL)
Production by Human Endometrial Stromal Cells in
Culture: Evidence for Trophoblast-Endometrial
Interaction Presented at the 38th Annual

Paracrine
Meeting of the

Pacific Coast Fertility Society
April 25-29, 1990, Scottsdale, Arizona

Mead Johnson Laboratory/Purvis Martin, M.D.
Research Award
Paper entitled: Insulin Induced Stress
Responses and the Effects of Estrogen and
Progestin in Postmenopausal Women (PMW)

Presented at the 39th Annual Meeting of the
Pacific Coast Fertility Society, April 10-14, 1991
Indian Wells, California

Serono Award (1st Prize)
Paper entitled: The Synergistic Effects of
Clomiphene Citrate and Human Menopausal
Gonadotropins in Folliculogenesis of Hyperstimulated
Cycles as Assessed by GnRH Antagonist (Nal-Glu)
Presented at the 39th Annual Meeting of the
Pacific Coast Fertility Society, April 10-14, 1991,
Indian Wells, California

Serono Award (1st Prize)
Paper entitled: Assessing the Pharmacodynamic
Properties of Exogenously Administered Progesterone:
A comparison of Micronized Vaginal Delivery to
Intramuscular Routes
Presented at the 40th Annual Meeting of the
Pacific Coast Fertility Society
April 8-12, 1992, Indian Wells, California

Mead Johnson Laboratory/Purvis Martin, M.D.,
Research Award
Paper entitled: The Route of Administration
Influences the Effect of Estrogen on Insulin Sensitivity in
Postmenopausal Women. Presented at the 41st Annual
Meeting of the Pacific Coast Fertility Society, April 14-18,
1993, Indian Wells, California

Serono Award (1st Prize)
Paper entitled: Serum AoG is a Useful Marker
for the Treatment of Acne in Normoandrogenic Women
Presented at the 42nd Annual Meeting of the
Pacific Coast Fertility Society, April 20-24, 1994
Indian Wells, California

PUBLICATIONS

Rogerio A. Lobo, M.D.

Peer-Review Journals:

1. Lobo RA, Kletzky OA, Kaptein EM and Goebelsmann U: Prolactin modulation of dehydroepiandrosterone sulfate secretion. Am J Obstet Gynecol 138:632-636, 1980.

2. Lobo RA, March CM, Goebelsmann U, Krauss RM and Mishell DR Jr: Sub-dermal estradiol pellets following hysterectomy and oophorectomy. Effect upon serum estrone, estradiol, luteinizing hormone, follicle-stimulating hormone, corticosteroid binding globulin-binding capacity, testosterone-estradiol binding globulin-binding capacity, lipids, and hot flushes. Am J Obstet Gynecol 138:714-719, 1980.

3. Lobo RA and Goebelsmann U: Adult manifestation of congenital adrenal hyperplasia due to incomplete 21-hydroxylase deficiency mimicking polycystic ovarian disease. Am J Obstet Gynecol 138:720-726, 1980.

4. Lobo RA, Paul WL and Goebelsmann U: Dehydroepiandrosterone sulfate as an indicator of adrenal androgen function. Obstet Gynecol 57:69-73, 1981.

5. Lobo RA, Granger L, Goebelsmann U and Mishell DR Jr: Elevations in unbound serum estradiol as a possible mechanism for inappropriate gonadotropin secretion in women with PCO. J Clin Endocrinol Metab 52:156-158, 1981.

6. Lobo RA, Paul WL and Goebelsmann U: Serum levels of DHEAS in gynecologic endocrinopathy and infertility. Obstet Gynecol 57:607-612, 1981.

7. Lobo RA and Goebelsmann U: Evidence for reduced 3ß-ol-hydroxysteroid dehydrogenase activity in some hirsute women thought to have polycystic ovary syndrome. J Clin Endocrinol Metab 53:394-400, 1981.

8. Lobo RA, March CM, Goebelsmann U and Mishell DR Jr: The modulating role of obesity and 17ß-estradiol (E_2) on bound and unbound E_2 and adrenal androgens in oophorectomized women. J Clin Endocrinol Metab 54:320-324, 1982.

9. Lobo RA, Gysler M, March CM, Goebelsmann U and Mishell DR Jr: Clinical and laboratory predictors of clomiphene response. Fertil Steril 37:168-174,1982.

10. Lobo RA and Goebelsmann U: Effect of androgen excess on inappropriate gonadotropin secretion as found in the polycystic ovary syndrome. Am J Obstet Gynecol 142:394-401, 1982.

11. Lobo RA, Goebelsmann U, Brenner PF and Mishell DR Jr: The effects of estrogen on adrenal androgens in oophorectomized women. Am J Obstet Gynecol 142:471-478, 1982.

12. Horton R, Hawks D and Lobo R: 3_α, 17ß-Androstanediol glucuronide in plasma: A marker of androgen action in idiopathic hirsutism. J Clin Invest 69:1203-1206, 1982.

13. Lobo RA, Granger LR, Davajan V and Mishell DR Jr: An extended regimen of clomiphene citrate in women unresponsive to standard therapy. Fertil Steril 37:762-766, 1982.

14. Lobo RA and Gibbons WE: The role of progestin therapy in breast disease and central nervous system function. J Reprod Med 27:515-521, 1982.

15. Lobo RA, Paul W, March CM, Granger L and Kletzky OA: Clomiphene and dexamethasone in women unresponsive to clomiphene alone. Obstet Gynecol 60:497-501, 1982.

16. Lahteenmaki P, Lobo R, Marrs RP, Gibbons WE, Nakamura RM and diZerega GS: Characterization of porcine granulosa cells by isopycnic gradient centrifugation. Biol Reprod 27:633-640, 1982.

17. Mashchak CA, Lobo RA, Dozono-Takano R, Eggena P, Nakamura RM, Brenner PF and Mishell DR Jr: Comparison of pharmacodynamic properties of various estrogen formulations. Am J Obstet Gynecol 144:511-518, 1982.

18. Shaaban MM, Hung TT, Hoffman DI, Lobo RA and Goebelsmann U: ß-Endorphin and ß-lipotropin concentrations in umbilical cord blood. Am J Obset Gynecol 144:560-568, 1982.

19. Readhead C, Lobo RA and Kletzky OA: The activity of 3ß-hydroxysteroid dehydrogenase and ∇^{4-5} isomerase in human follicular tissue. Am J Obstet Gynecol 145:491-495, 1983.

20. Lobo RA, Granger LR, Paul WL, Goebelsmann U and Mishell DR Jr: Psychological stress and increases in urinary norepinephrine metabolites, platelet serotonin, and adrenal androgens in women with polycystic ovary syndrome. Am J Obstet Gynecol 145:496-503, 1983.

21. Lobo RA and Kletzky OA: Normalization of androgen and sex hormone-binding globulin levels after treatment of hyperprolactinemia. J Clin Endocrinol Metab 56:562-566, 1983.

22. Lobo RA, Kletzky OA, Campeau JD and diZerega GS: Elevated bioactive luteinizing hormone in women with the polycystic ovary syndrome. Fertil Steril 39:674-678, 1983.

23. Petrucha RA, Goebelsmann U, Hung TT, Haase HR and Lobo RA: Amniotic fluid ß-endorphin and ß-lipotropin concentrations during the second and third trimester. Am J Obstet Gynecol 146:644-651, 1983.

24. Lobo RA, Brenner P and Mishell DR Jr: Metabolic parameters and steroid levels in postmenopausal women receiving lower doses of natural estrogen replacement. Obstet

Gynecol 62:94-98, 1983.

25. Lobo RA, Goebelsmann U and Horton R: Evidence for the importance of peripheral tissue events in the development of hirsutism in polycystic ovary syndrome. J Clin Endocrinol Metab 57:393-397, 1983.

26. diZerega GS, Campeau JD, Nakamura RM, Ujita EL, Lobo R and Marrs RP: Activity of a human follicular fluid protein(s) in spontaneous and induced ovarian cycles. J. Clin Endocrinol Metab 57:838-846, 1983.

27. Shoupe D, Kumar DD and Lobo R: Insulin resistance in polycystic ovary syndrome. Am J Obstet Gynecol 147:588-592, 1983.

28. diZerega GS, Campeau JD, Ujita EL, Kling OR, Marrs RP, Lobo RA and Nakamura RM: The possible role for a follicular protein in the intraovarian regulation of folliculogenesis. Sem Reprod Endocrinol 1:309-320, 1983.

29. Lobo RA, McCormick W, Singer F and Roy S: Depo-medroxyprogesterone acetate compared with conjugated estrogens for the treatment of postmenopausal women. Obstet Gynecol 63:1-5, 1984.

30. Lobo RA, Shoupe D, Chang SP and Campeau J: The control of bioactive luteinizing hormone secretion in women with polycystic ovary syndrome. Am J Obstet Gynecol 148:423-428, 1984.

31. Shoupe D, and Lobo RA: The influence of androgens on insulin resistance. Fertil Steril 41:385-388, 1984.

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17. Granger LR, Lobo RA and Mishell DR Jr: An extended regimen of clomiphene citrate in women unresponsive to standard therapy. Presented at the 29th Annual Meeting of the Pacific Coast Fertility Society, October 14-18, 1981, Rancho Mirage, California.

18. Lobo RA, Granger LR, Paul WL, Goebelsmann U and Mishell DR Jr: The relationship between psychological stress, neuro-transmitters and androgen secretion in women with PCO. Presented at the 29th Annual Meeting of the Pacific Coast Fertility Society, October 14-18, 1981, Rancho Mirage, California.

19. Lahteenmaki P, Lobo R, Marrs RP, Gibbons WE, Nakamura RM and diZerega GS: folliculogenesis in response to clomiphene therapy: Allochronic follicular maturation.

Presented at the 29th Annual Meeting of the Pacific Coast Fertility Society, October 14-18, 1981, Rancho Mirage, California.

20. Horton R, Lobo R and Hawks D: Plasma androstanediol glucuronide (3_{α}diol G), a marker of peripheral androgen action in hirsutism. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 16-19, 1982, Carmel, California.

21. Horton R, Lobo R and Hawks D: Androstanediol glucuronide (3_{α}-diol G) in plasma: A measure of peripheral androgen action. Presented at the 7th Annual Meeting of The American Society of Andrology, February 23-26, 1982, Hilton Head Island, Southern California.

22. Lobo RA, Kletzky OA and diZerega GS: Elevated serum bioactive luteinizing hormone (LH) concentrations in women with polycystic ovary syndrome (PCO). Presented at the 38th Annual Meeting of The American Fertility Society, March 20-24, 1982, Las Vegas, Nevada.

23. Lobo RA and Kletzky OA: Elevated androgen levels and decreased SHBG in hyperprolactinemia. Presented at the 29th Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.

24. Gibbons WE, Lobo RA, Roy S and Mishell DR Jr: Estrogen receptor levels in the endometria of post-menopausal women on estrogen and progestin replacement. Presented at the 29th Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.

25. Lobo RA, Hung TT, diZerega GS, Kletzky OA and Goebelsmann U: Control of adrenal androgen secretion in women with PCO. Presented at the 29th Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.

26. Lobo RA, Goebelsmann U and Horton R: 5_{α}-androstane-3_{α}, 17β-diol-3-glucuronide (3_{α}AG), an index of increased peripheral androgen action in hirsutism. Presented at the 29th Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.

27. Lobo RA, Hung TT, Roy S and Goebelsmann U: Estrogen therapy raises serum dehydroepiandrosterone sulfate (DHEA-S) in oophorectomized (OO) women through mechanisms independent of ACTH or β-EP). Presented at the 29th Annual Meeting of the Society for Gynecologic Investigation, March 24-27, Dallas, Texas.

28. Petrucha RA, Hung TT, Lobo RA and Goebelsmann U: Amniotic fluid (AF) β-endorphin β-lipotropin (β-EP) and β-LPH) concentrations during the second and third trimester.

Presented at the 29th Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 1982, Dallas, Texas.

29. Goebelsmann U, Shaaban MM, Hung TT, Hoffman DI and Lobo RA: Beta-endorphin (β- EP) and β-lipotropin (β-LPH) in human. Presented at the 29th Annual Meeting of the Society for Gynecologic Investigation, March 24-27, 19982, Dallas, Texas.

30. Horton R, Lobo R and Hawks D. Androstanediol glucuronide in plasma, a marker of androgen action in men and women. Presented at the 74th Annual Meeting of the American Federation for Clinical Research, American Society for Clinical Investigation, May 8-10, 1982, Washington, D.C.

31. Lahteenmaki P, Lobo R, Marrs R, Gibbons W, Nakamura R and diZerega G: Characterization of porcine granulosa cells by isopycnic gradient centrifugation. Presented at the 64th Annual Meeting of The Endocrine Society, June 16-18, 1982, San Francisco, California.

32. Lobo RA, Goebelsmann U and Horton R: Hirsutism in polycystic ovary syndrome (PCO). Presented at the 30th Annual Meeting of the Pacific Coast Fertility Society, October 13-17, 1982, Scottsdale, Arizona.

33. Montoro M, Kletzky OA, Lobo R and Nicoloff JT: Altered pituitary function in women and men with pituitary hypothyroidism. Presented at the 30th Annual Meeting of the Pacific Coast Fertility Society, October 13-17, 1982, Scottsdale, Arizona.

34. Moghissi E, Lobo R, Hawks D and Horton R: Evidence for peripheral factors in the hirsutism of the polycystic ovary syndrome. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 9-11, 1983, Carmel, California.

35. Fallis R, Fisher M and Lobo R: A double-blind trial of naloxone in acute stroke. Presented at the Eight International Joint Conference on Stroke and Cerebral Circulation, February 10-12, 1983, San Diego, California.

36. Lobo R and Shoupe D; Evidence for decreased dopaminergic control of LH secretion in polycystic ovary syndrome (PCO): Presented at the 30th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D. C.

37. Shoupe D, Campeau J and Lobo RA: Differences in bioactive (bio) LH and immunoreactive (I) LH secretion in women. Presented at the 30th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.

38. Marrs RP, Lobo R, Campeau JD, Brown J and diZerega GS: Correlation of human follicular fluid inhibin activity with spontaneous and induced follicular development. Presented at the 30th Annual Meeting of the Society for Gynecologic Investigation, March

17-20, 1983, Washington, D.C.

39. Vargyas J and Lobo R: The role of non-SHBG bound estradiol (E2), total E2, progesterone (P) and the E2/P ratio in the premenstrual syndrome (PMS). Presented at the 30th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.

40. Gibbons WE, Lobo RA, Moyer DL, Roy S and Mishell DR Jr; A comparison of biochemical and morphological events mediated by estrogen ± progestin in the endometrium of postmenopausal women. Presented at the 30th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.

41. Shoupe D, Kumar D and Lobo R: Insulin resistance in polycystic ovary syndrome (PCO). Presented at the 30th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1983, Washington, D.C.

42. Lobo RA, Goebelsmann U and Horton R: Evidence for peripheral factors in the development of hirsutism in polycystic ovary syndrome. Presented at the 39th Annual Meeting of The American Fertility Society, April 16-20, 1983, San Francisco, California.

43. Shoupe D and Lobo RA: Insulin resistance in polycystic ovary syndrome (PCO). Presented at the 39th Annual Meeting of The American Fertility Society, April 16-20, 1983, San Francisco, California.

44. Hoffman DI and Lobo RA: The prevalence and significance of elevated DHEA-S levels in anovulatory women. Presented at the 39th Annual Meeting of The American Fertility Society, April 16-20, 1983, San Francisco, California.

45. Shoupe D and Lobo RA: Decreased dopaminergic control of LH secretion in polycystic ovary syndrome (PCO) yet differences in the control of immunological (I) LH and bioactive (bio) LH. Presented at the 65th Annual Meting of The Endocrine Society, June 8-10, 1983, San Antonio, TX.

46. Marrs RP, Vargyas JM and Lobo R: Comparison of the intrafollicular hormone milieu with fertilization of human oocytes in vitro. Presented at the 65th Annual Meeting of The Endocrine Society, June 8-10, 1983, San Antonio, Texas.

47. Lobo RA, Vargyas JM and Marrs RP: Androgen levels in follicular fluid (FF) and its relationship to the maturity of the oocyte and its ability to be fertilized in vitro. Presented at t the 31st Annual Meeting of the Pacific Coast Fertility Society, October 12-16, 1983, Rancho Mirage, California.

48. Ablan F, Moghissi M, Hoopes M, Lobo RA and Horton R: Origin of androstanediol glucuronide in plasma of men and women with polycystic ovary syndrome. Presented at the annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 8-10, 1984, Carmel, California.

49. Serafini P and Lobo R; Androgenicity in women; Tissue 5_{α}-reductase activity (5_{α}-RA) and serum androgen levels. Presented at the 31st Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.

50. Serafini P and Lobo R: Hirsutism in postmenopausal women (PoW): Androgen/estrogen ratios and 5_{α}-reductase activity (5_{α}-RA). Presented at the 31st Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.

51. Shoupe D, Chang SP, Kletzky OA and Lobo R: Differences in the ratio of bioactive to immunoreactive serum LH during vasomotor flushes and hormonal therapy in postmenopausal women. Presented at the 31st Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.

52. Shoupe D, Montz FJ and Lobo R: LH and PRL-evoked naloxone (Nal) responses and plasma β-EP in oophorectomized women (Ow) before and after estrogen (E) and progestin (P) treatment. Presented at the 31st Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1984, San Francisco, California.

53. Serafini P, Goebelsmann UT and Lobo RA: Increased 5_{α}-reductase activity in hirsutism. Presented at the 40th Annual Meeting of The American Fertility Society, April 2-7, 1984, New Orleans, Louisiana.

54. Lobo R, Shoupe D, Serafini P, Brinton D and Horton R: Serum androgens and the clinical response to spironolactone therapy. Presented at the 40th Annual Meeting of The American Fertility Society, April 2-7, 1984, New Orleans, Louisiana.

55. Shoupe D and Lobo RA: PRL responses after GnRH in PCO. Presented at the 40th Annual Meeting of The American Fertility Society, April 2-7, 1984, New Orleans, Louisiana.

56. Serafini P, Ablan F, Horton R and Lobo R: The effects of spironolactone and progesterone on in vitro 5_{α}-reductase activity in hirsute women. Presented at the International Symposium on Regulation of Androgen Action, June 29-July 1, 1984, Montreal, Quebec, Canada.

57. Serafini P, Ablan F and Lobo R: Increased in vitro production of DHT-glucuronide (G) and 3_{α}- androstanediol (3_{α}-diol) G from the skin of hirsute women. Presented at the 7th International Congress of Endocrinology, July 1-7, 1984. Quebec City, Quebec, Canada.

58. Shoupe D, Barnes RB, Montz FJ, Brazal SD and Lobo R: Bioactive (bio) LH and the bio: immunoreactive (i) LH ratio after naloxone (nal) as a probe for endogenous central opioid activity (COA) in women. Presented at the 7th International Congress of Endocrinology, July 1-7, 1984, Quebec City, Quebec, Canada.

59. Barnes R, Shoupe D and Lobo R: Endogenous opioid activity in polycystic ovary syndrome. Presented at the 7th International Congress of Endocrinology, July 1-7, 1984, Quebec City, Quebec, Canada.

60. Hoffman D, Lobo R, Platt L and diZerega G: Differential follicular response in anovulatory patients to purified urinary FSH versus purified urinary FSH and LH. Presented at the Vth Reinier de Graaf Symposium: Gamete Quality and Fertility Regulation, August 23-25, 1984, Nijmegen, The Netherlands.

61. Serafini P and Lobo R: The effects of spironolactone on adrenal steroidogenesis in hirsute women. Presented at the 32nd Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.

62. Barnes R, Shoupe D, Chiang J and Lobo R: Central opioid activity in polycystic ovary syndrome. Presented at the 32nd Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.

63. Vargyas J, Lobo R and Mishell D: Brain opioid activity in the premenstrual cycle. Presented at the 32nd Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984.

64. Hoffman DI, Lobo R, Moyer D, Roy S and Platt L: Evaluation of early follicular phase administration of a potent gonadotropin-releasing hormone agonist (Wy-40, 972, Wyeth). Presented at the 32nd Annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.

65. Steingold KA, Lobo R, Andrews L, Lu JKH, Judd HL and Chang RJ: The effect of bromocriptine on gonadotropin secretion in polycystic ovary disease. Presented at the 32nd annual Meeting of the Pacific Coast Fertility Society, September 19-23, 1984, Rancho Mirage, California.

66. Lobo RA and Serafini PC: Peripheral androgen metabolism (PAM) in postmenopausal (PM) women and the complaint of hirsutism. Presented at The Fourth International Congress on the Menopause, October 28-November 2, 1984, Orlando, Florida.

67. Barnes R, Roy S and Lobo R: Plasma lipid and serum androgen levels in postmenopausal (PM) women treated with depo-medroxyprogesterone acetate (DMPA). Presented at The Fourth International Congress on the Menopause, October 28-november 2, 1984, Orlando, Florida.

68. Serafini P, Paulson F, Elkind-Hirsch K, Hernandez M and Lobo R: Acute modulation of the hypothalamic pituitary axis (HPA) by testosterone (T) in normal women. Presented at the 32nd Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, phoenix, Arizona.

69. Baranes R, Cha K and Lobo R: Altered dopaminergic control of PRL in polycystic ovary syndrome (PCO). Presented at the 32nd Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, Phoenix, Arizona.

70. Barnes R, Lee D and Lobo R: Dopamine but not norepinephrine influences the bioactivity of LH in normal women. Presented at the 32nd Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, Phoenix, Arizona.

71. Paulson R, Serafini P, Catalino J and Lobo R: Serum and urinary 3 α-androstanediol glucuronide 3α-diol G) and their correlations with genital skin 5α-reductase activity (5αRA) and 3α-diol G formation. Presented at the 32nd Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1985, Phoenix, Arizona.

72. Baranes RB, Chiang JH, Cha KY, Shoupe D and Lobo R: Responses of bio and iLH and FSH to 2 doses of a nasal GnRH agonist. Presented at the 33rd Annual Meeting of the Pacific Coast Fertility Society, April 24-28, 1985, Las Vegas, Nevada.

73. Paulson RJ, Bernstein GS and Lobo RA: Idiopathic oligospermia and peripheral androgen metabolism. Presented at the 33rd Annual Meeting of the Pacific Coast Fertility Society, April 24-28, 1985, Las Vegas, Nevada.

74. Serafini PC and Lobo RA: Prolactin (PRL) modulates peripheral androgen metabolism (PAM). Presented at the 33rd Annual Meeting of the Pacific Coast Fertility Society, April 24-28, 1985, Las Vegas, Nevada.

75. Serafini P, Paulson R, Francis M and Lobo R: Testosterone elicits divergent PRL and LH responses after GnRH in normal women. Presented at the 67th Annual Meeting of The Endocrine Society, June 19-21, 1985, Baltimore, Maryland.

76. Barnes R, Artal R and Lobo R: Altered catecholamine metabolism in polycystic ovary syndrome (PCO). Presented at the 67th Annual Meeting of The Endocrine Society, June 19-21, 1985, Baltimore, Maryland.

77. Greep N, Hoopes M, Lobo R and Horton R: Evidence for a role of androstenedione as precursor of plasma DHT and androstanediol glucuronide in normal hirsute women.

Presented at the 67th Annual Meeting of The Endocrine Society, June 19-21, 1985, Baltimore, Maryland.

78. Lobo RA, Serafini PC and Paulson RJ: Genital skin 5_{α}-reductase activity (5_{α}RA): A marker of androgenicity in women. Presented at the 4th Annual Meeting of The American Gynecological and Obstetrical Society, September 4-7, 1985, Hot Springs, Virginia.

79. Mileikowsky G, Anderson R, Chen D, Siegel M and Lobo R: Radionuclide hysterosalpingo tomography (RHST) for the evaluation of the reproductive tract in infertility. Presented at the 41st Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.

80. Barnes R, Spencer C and Lobo R: Responses of LH, PRL and TSH to dopaminergic blockade in polycystic ovary syndrome (PCO): Lack of evidence for decreased dopaminergic activity. Presented at the 41st Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.

81. Cha K, Barnes R, Marrs R and Lobo R: Oocyte maturity in the spontaneous cycle correlates with follicular fluid (FF) progesterone (Prog) levels and LH of greater biological activity. Presented at the 41st Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.

82. Paulson R, Serafini P and Lobo R: Effect of sex steroids on 5_{α}-reductase activity (5_{α}RA) in vitro. Presented at the 41st Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.

83. Hoffman D, Lobo R, Campeau J and diZerega G: Increased prolactin (PRL) levels in gonadotropin-stimulated cycles. Presented at the 41st Annual Meeting of The American Fertility Society, September 27-October 2, 1985, Chicago, Illinois.

84. Cha K, Campeau J, Marrs R, Nakamura R and Lobo R: Follicular fluid (FF) LH bioactivity and oocyte maturity (OM) in spontaneous (S) and stimulated (STIM) cycles. Presented at the 33rd Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.

85. Paulson RJ, Paulson YJ, Silva PD, Cha KY, Lobo RA, Yee B and Marrs RP: Hormonal dynamics of hCG-triggered ovulation: Bio-hCG and steroid response. Presented at the 33rd Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.

86. Shoupe D, Spitz I, Osborn C, Page M, Mishell D Jr and Lobo R: Effects of progesterone (P) antagonism on gonadotropins at midcycle and during the luteal phase. Presented at the 33rd Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.

87. Silva P, Paulson R, Serafini P, Francis M and Lobo R: Acute effects of testosterone (T) on immunoreactive luteinizing hormone (ILH) and bioreactive LH (BLH) in normal women. Program book of the 33rd Annual Meeting of the Society for Gynecologic Investigation, March 19-22, Toronto, Ontario, Canada.

88. Paulson R, Gentzschein E Nguyen H and Lobo R: Differences between genital skin (G) and pubic (P) skin 5_{α}-reductase activity (5_{α}RA). Program book of the 33rd Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1986, Toronto, Ontario, Canada.

89. Silva P, Gentzschein E, Paulson R, Horton R and Lobo R: Androstenedione (A) as precursor for DHT: Evidence for dissociated blood and tissue DHT production (P). Program book of the 33rd Annual Meeting of the Society for Gynecologic Investigation, March 19-22, 1996, Toronto, Ontario, Canada.

90. Paulson RJ, Silva PD, Paulson YJ, Cha KY, Yee B, Lobo RA and Marrs RP: The effects of different doses of intramuscular hCH on follicular fluid (FF) steroid and hCG levels and on oocyte maturity (OM). Presented at the 34th Annual Meeting of the Pacific Coast Fertility Society, April 9-13, 1986, San Diego, California.

91. Rosen GF, Vermesh M, Gentzschein E and Lobo RA: Clinical heterogeneity in Turner's syndrome. Presented at the 34th Annual Meeting of the Pacific Coast Fertility Society, April 9-13, 1986, San Diego, California.

92. Silva PD, Porto M, Moyer DL and Lobo RA: Expression of androgenicity in a nonsteroid secreting tumor in pregnancy. Presented at the 34th Annual Meeting of the Pacific Coast Fertility Society, 9-13, 1986, San Diego, California.

93. Rosen GF and Lobo RA: Further evidence against dopamine (DA) deficiency as a cause of inappropriate gonadotropin secretion (IGS) in polycystic ovary syndrome (PCO). Presented at the 42nd Annual Meeting of The American Fertility Society/Canadian Fertility and Andrology Society, September 27-October 2, 1986, Toronto, Ontario, Canada.

94. Silva PD and Lobo RA: Androstenedione (A) is the major precursor of tissue dihydrotestosterone (DHT)-production (P) in women. Presented at the 42nd Annual Meeting of The American Fertility Society/Canadian Fertility and Andrology Society, September 27- October 2, 1986, Toronto, Ontario, Canada.

95. Rosen GF, Cha K-Y, Marrs RP and Lobo RA: Effects of pure FSH (Metrodin) and HCG on hormonal characteristics on follicular fluid (FF) and their correlation with oocyte maturity (OM). Presented at the 42nd Annual Meeting of The American Fertility Society/Canadian Fertility and Andrology Society, September 27-October 2, 1986, Toronto, Ontario, Canada.

96. Xu YK, Ng, WG, Kaufman F, Lobo R and Donnell GN: Galactose metabolism in human

ovary. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Pediatric Research, February 3-6, 1987, Carmel, California.

97. Pasupuleti V, Lobo R and Horton R: Formation of androstanediol glucuronide by human sexual skin. Presented at the Annual Meeting of the American Federation for Clinical Research, Western Society for Clinical Research, February 3-6, 1987, Carmel, California.

98. Lobo R, Gentzscheiin E, Pasupuleti V and Horton R: Differential pathways of 3$_\alpha$diol G) formation in human skin. Presented at the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

99. Vermesh M, Silva PD and Lobo R: Opiates modulate the inhibitory effect of androgen on the hypothalamic-pituitary axis (HPA) of normal women. Presented at the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

100. Davidson A, Vermesh M, Vijod A, Paulson RJ and Lobo R: Presence of immunoreactive β-endorphin (iβEP) in seminal plasma (SP) and its possible involvement in sperm motility. Presented at the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18- 21, 1987, Atlanta, Georgia.

101. Kaufman F, Xu Y, Ng W, Donnell G and Lobo R: Characterization of ovarian failure in galactosemia (G) and galactose (gal) metabolism in the ovary. Presented at the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

102. Lobo R, Nguyen H, Eggena P and Brenner P: Biological effects of equilin sulfate (EqS): Differences in hepatic and bone resorbing effects. Presented at the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

103. Paulson RJ, Do Y, Hsueh W, Eggena P and Lobo R: Prorenin (PR), renin activity (RA) and renin substrate (RS) in follicular fluid (FF): Correlation with oocyte maturity (OM) and FF steroids. Presented at the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

104. Shoupe D, Roy S and Lobo RA: Psychological function (Psy) and peripheral and central opioid activity (COA) in postmenopausal women (PM): Estrogen and progestin effects. Presented at the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

105. Vermesh M, Silva PD, Rosen GF and Lobo R: Induction of partial 21-hydroxylase deficiency by androgen in normal women. Program book of the 34th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1987, Atlanta, Georgia.

106. Davidson A, Vermesh M, Toker R, Braxton P, Lobo R and Paulson R: Mouse embryo culture as quality control for human IVF: The once cell (1C) vs. two cell (2C) model. Presented at the Vth World Congress - In Vitro Fertilization and Embryo Transfer, April 5-10, 1987, Norfolk, Virginia.

107. Lobo RA, Cristo M and Crary W: Effects of estrogen on psychological function in asymptomatic postmenopausal women. Presented at the Fifth International Congress on the Menopause, April 6-10, 1987, Sorrento, Italy.

108. Nguyen HN, Eggena P and Lobo RA: Biological effects of equilin sulfate; Differences in hepatic and bone resorbing effects. Presented at the Fifth International Congress on the Menopause, April 6-10, 1987, Sorrento, Italy.

109. Morton J, Fraser D, Whitehead MI and Lobo R: Is failure of progesterone action upon the endometrium due to poor end-organ response or to poor absorption/rapid metabolism of the progestogen? Presented at the Fifth International Congress on the Menopause, April 6-10, 1987, Sorrento, Italy.

110. Anderson RE, Ben-Rafael Z, Meloni L, Flickinger M, Barnes RB, Rosen GF and Lobo RA: Secretory dynamics of bioactive and immunoreactive PRL in PCO. Presented at the 35th Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.

111. Davidson A, Vermesh M, Lobo RA and Paulson RJ: The temporal effects of changes in IVF culture media on the one-cell (1C) mouse embryo system. Presented at the 35th Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.

112. Davidson A, Vermesh M, Vijod AG, Paulson RJ and Lobo RA: The presence of calcitonin in seminal plasma. Presented at the 35th Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.

113. Silva PD, Paulson RJ, Anderson RE, Werlin LB, Stein AL and Lobo RA: Ectopic pregnancy in contralateral tubal remnants after unilateral tubal anastomosis: Preventable and unpreventable causes. Presented at the 35th Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.

114. Stein A, Manoogian C, Vijod A and Lobo R: Adrenal androgen excess resulting in virilization and PCO-like features. Presented at the 35th Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.

115. Vermesh M, Silva PD, Rosen GF and Lobo RA: Adrenal effects of short-term administration of testosterone in normal women. Presented at the 35th Annual Meeting of the Pacific Coast Fertility Society, May 6-10, 1987, Palm Springs, California.

116. Stanczyk FZ, Kaufman FR, Gentzschein E and Lobo RA: Androstenedione (A) is an important precursor of dihydro-testosterone (DHT) in the skin of women and is metabolized via 5_{α}-androstenedione (5_{α}-A). Presented t the 69th Annual Meeting of The Endocrine Society, June 10-12, 1987, Indianapolis, Indiana.

117. Shoupe D, Mishell DR Jr, Tonetta SA, Spitz IM, Madkour H and Lobo RA: Suppression of ovulation by follicular phase administration of the antiprogestin RU 486 and evidence for suppression of ovarian steroidogenesis. Presented at the 69th Annual Meeting of The Endocrine Society, June 10-12, 1987, Indianapolis, Indiana.

118. Pasupuleti V, Lobo R and Horton R: Conversion of dihydrotestosterone to androstanediol glucuronide by skin. Presented at the 69th Annual Meeting of The Endocrine Society, June 10-12, 1987, Indianapolis, Indiana.

119. Davidson A, Vermesh M, Lobo RA and Paulson RJ: The temporal effects of changes in IVF culture media on the one-cell (1C) mouse embryo system. Presented at the 43rd Annual Meeting of The American Fertility Society, September 28-30, 1987, Reno, Nevada.

120. Stein AL and Lobo RA: Factors determining clitoral hypertrophy (CH) in hyperandrogenism. Presented at the 43rd Annual Meeting of The American Fertility Society, September 28-30, 1987, Reno, Nevada.

121. Anderson R, Cragun J, Chang RJ, Bhasin S, Stanczyk F, Vijod M and Lobo RA: Pharmacodynamics of human urinary FSH (hFSH) and human menopausal gonadotropin hMG) in PCO and normal women. Presented at the 35th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.

122. Shoupe D, Mishell DR Jr and Lobo R: Evidence that oxytocin increases cortisol secretion and decreases LH pulsatility in normal women. Presented at the 35th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.

123. Matteri RK, Stanczyk FZ, Kaufman FR, Vijod AG, Anderson RE and Lobo RA: Measurement and comparison of circulating C19 sulfates and glucuronides in normal and hirsute women and men. Presented at the 35th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.

124. Paulson RJ, Do Y, Hsueh W and Lobo R: Prorenin (PR) and renin activity (RA) in ovarian venous (OV) and peripheral venous (PV) blood: Gradients and correlations with ovarian steroids. Presented at the 35th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.

125. Kaufman FR, Matteri RK, Stanczyk FZ, Gentzschein E, Delgado C and Lobo RA: Characterization of dehydroepiandrosterone (DHEA) and DHEA-sulfate (S) metabolism

in

human genital skin. Presented at the 35th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.

126. Stanczyk FZ, Shoupe D, Nunez V and Lobo RA: A randomized comparison of non-oral estradiol (E2) delivery in post-menopausal women (PM). Presented at the 35th Annual Meeting of the Society for Gynecologic Investigation, March 17-20, 1988, Baltimore, Maryland.

127. Matteri RK, Stanczyk FZ, Kaufman FR, Chenette PE, Anderson RE, Gentzschein E and Lobo RA: Androgen sulfates as markers of peripheral androgen action in hirsutism. Presented at the 36th Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.

128. Anderson RE, Stein AL, Paulson RJ and Lobo RA: Effects of norethindrone (NET) used to program oocyte retrieval for in vitro fertilization. Presented at the 36th Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.

129. Shoupe D, Mishell DR, Lobo RA, Lacarra M, Horenstein J, d'Ablaining G, Moyer D: Correlation of endometrial maturation with 4 methods of estimating day of ovulation. Presented at the 36th Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.

130. Graczykowski JW, Vermesh M, Siegel MS and Lobo RA: The effect of beta-endorphin (β-EP) and calcitonin (CT) on sperm movement characteristics in vitro. Presented at the 36th Annual Meeting of the Pacific Coast Fertility Society, April 13-17, 1988, Palm Springs, California.

131 Matteri RK, Stanczyk FZ, Kaufman FR, Delgado C, Gentzschein E and Lobo RA: Production of C19 sulfates and glucuronides in human genital skin. Presented at the 70th Annual Meeting of The Endocrine Society, June 8-11, 1988, New Orleans, Louisiana.

132 Carmina E, Malizia G, Janni A and Lobo RA: Comparison of adrenal responses with ACTH and ovine (O) CRF in normal and hyperandrogenic women. Presented at the 70th Annual Meeting of The Endocrine Society, June 8-11, 1988, New Orleans, Louisiana.

133. Matteri R, Hatch I, Delgado C, Paulson R, Stanczyk F and Lobo R: Influence of the ovary on androgens of peripheral origin. Presented at the 44th Annual Meeting of The American Fertility Society, October 8-13, 1988, Atlanta, Georgia.

134. Anderson RE, Paulson RJ, Sauer MV and Lobo RA: Evidence supporting the routine use of a GnRH agonist (GnRH-a) during ovarian stimulation for in vitro fertilization (IVF). Presented at the 4th Annual Meeting of The American Fertility Society, October 8-13, 1988, Atlanta, Georgia.

135. Vermesh M, Silva PD, Rosen GF, Stein AL, Fossum GT, Anderson RE, Sauer MV,

Vargyas JM, Lobo RA and Mishell DR Jr: Management of unruptured ectopic pregnancy (UEP) by linear salpingostomy (LS). An extended, prospective clinical trial of laparoscopy (LSC) versus laparotomy. Presented at the 44th Annual Meeting of the American Fertility Society, October 8-13, 1988, Atlanta, Georgia.

136. Levin JH, Anderson RE, Stanczyk FZ and Lobo RA: Characteristics of progestin (P) inhibition of gonadotropin secretion in normal women. Presented at the 36th Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.

137. Matteri RK, Stanczyk FZ, Lee DG, Delgado C, Gentzschein E and Lobo RA: C-19 conjugates reflect both ovarian and peripheral androgen metabolism. Presented at the 36th Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.

138. Matteri RK, Stanczyk FZ, Gentzschein E, Vijod AG and Lobo RA: Δ^5 androstenediol and its conjugates in pre and post-menopausal women and men. Presented at the 36th Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.

139. Stanczyk FZ, Nadler J, Vijod AG, Krikorian L, Rosen GF, Steinleitner A and Lobo RA: Influence of estrogen and the effect of smoking on prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) balance in postmenopausal women. Presented at the 36th Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.

140. Steinleitner A, Stanczyk FZ, Levin JH, Vijod MA, Nakamura RM and Lobo RA: Decreased production of 6-keto-prostaglandin ($F_{1\alpha}$) ($6KPGF_{1\alpha}$) by postmenopausal uterine arteries. Presented at the 36th Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.

141. Steinleitner A, Stanczyk FZ, Paulson RJ and Lobo RA: Characterization of proopiomelanocortin (POMC) peptides in porcine and human follicular fluid. Presented at the 36th Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.

142. Paulson RJ, Hernandez MF, Do YS, Hsueh WA and Lobo RA: Angiotensin II (AII) modulation of steroidogenesis by luteinized granulosa cells in vitro. Presented at the 36th Annual Meeting of the Society for Gynecologic Investigation, March 15-18, 1989, San Diego, California.

143. Carmina E, Levin JH, Malizia G and Lobo RA: Decreased responses of ACTH to ovine corticotropin-releasing factor (oCRF) and increased adrenal insensitivity in hyperandrogenic women. Presented at the 37th Annual Meeting of the Pacific Coast Fertility Society, April 12-16, 1989, Palm Springs, California.

144. Paulson RJ, Francis-Hernandez M, Macaso TM, Lobo RA and Sauer MV: Embryo

implantation following human in vitro fertilization (IVF): Relative contributions of embryo quality (EQ) and endometrial receptivity (ER). Presented at the 37th Annual Meeting of the Pacific Coast Fertility Society, April 12-16, 1989, Palm Springs, California.

145. Sauer MV, Macaso TM, Francis-Hernandez M, Lobo RA and Paulson RJ: Establishment of a non-anonymous donor oocyte program: Preliminary experience at the University of Southern California. Presented at the 37th Annual Meeting of the Pacific Coast Fertility Society, April 12-16, 1989, Palm Springs, California.

146. Carmina E, Levin JH and Lobo RA: Clinical similarities between late onset congenital adrenal hyperplasia and polycystic ovary syndrome. Presented at the 71st Annual Meeting of The Endocrine Society, June 21-24, 1989, Seattle, Washington.

147. Matteri RK, Kaufman FR, Stanczyk FZ, Gentzschein E, Vijod AG and Lobo RA: Androgens of peripheral origin increase during adrenarche in boys. Presented at the 71st Annual Meeting of The Endocrine Society, June 21-24, 1989, Seattle, Washington.

148. Matteri RK, Levin JH, Stanczyk FZ, Paulson RJ and Lobo RA: Androgens are elevated with gonadotropin therapy despite GnRH-agonist suppression. Presented at the 45th Annual Meeting of The American Fertility Society, November 11-16, 1989, San Francisco, California.

149. Carmina E, Stanczyk FZ, Matteri RK and Lobo RA: Androsterone glucuronide signifies the presence and severity of acne (A) among hyperandrogenic hirsute women (HHW). Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

150. Lee DG, Pike MC, Stanczyk FZ and Lobo RA: A reevaluation of the effects of smoking on estrogen status. Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

151. Presser SC, Stanczyk FZ and Lobo RA: The simultaneous measurements of prostacyclin and thromboxane metabolites during the menstrual cycle and in postmenopausal women. Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

152. Levin, JH, Tonetta SA, Hickey MJ and Lobo RA; Growth factors modulate prolactin (PRL) production by isolated, dispersed human endometrial stromal cells in culture. Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

153. Levin JH, Tonetta SA, Stanczyk FZ and Lobo RA: Differential regulation of prolactin (PRL) and prostacyclin production by human endometrial stromal cells in culture.

Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

154. Levin JH, Hickey MJ and Lobo RA: Mechanisms of clomiphene citrate (CC) resistance in polycystic ovary syndrome (PCO). Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

155. Stanczyk FZ, Moltz L, Schwartz U and Lobo RA: Dexamethasone (DEX) suppressibility and adrenal and ovarian venous effluents of 5_{α}-reduced C19 conjugates in women. Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

156. Steinleitner A, Stanczyk FZ and Lobo RA: Production of POMC peptides under gonadotropin stimulation and modulation of ovarian steroidogenesis by POMC peptides in cultured porcine granulosa cells (pGC). Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

157. Sauer MV, Paulson RJ and Lobo RA: Oocyte donation: Extending reproductive potential to women over forty. Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

158. Paulson RJ, Sauer MV and Lobo RA: Factors affecting embryo implantation (EI) following human in vitro fertilization (IVF). Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

159. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: In vitro fertilization (IVF) in unstimulated cycles. Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

160. Price T, Dupuis R, Pollack G, Mattern W, Stanczyk F, Lobo R, Dotters D and Droegemueller W: Single dose pharmacokinetics of a 35 μg ethinyl estradiol, 1 mg norethindrone combination oral contraceptive in women with chronic renal failure on continuous ambulatory peritoneal dialysis. Presented at the 37th Annual Meeting of the Society for gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

161. Kovacs BW, Kornafel K, Shahbahrami B, Curtain J and Lobo R: Molecular alterations in endometrial hyperplasias and cancers. Presented at the 37th Annual Meeting of the Society for Gynecologic Investigation, March 21-24, 1990, St. Louis, Missouri.

162. Sauer MV, Paulson RJ, Macaso TM, Francis MM and Lobo RA: Nonanonymous oocyte donation: A successful treatment for infertility in women with ovarian failure. Presented at the 38th Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.

163. Frederick JL, Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: In vitro fertilization (IVF) in unstimulated cycles: Analysis of follicular fluid (FF) steroids.

Presented at the 38th Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.

164. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Use of test-yolk buffer (TYB) to enhance fertilization during human in vitro fertilization (IVF) in cases of suspected male infertility. Presented at the 38th Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.

165. Levin JH, Tonetta SA and Lobo RA: Human chorionic gonadotropin (hCG) enhances progestin stimulation of prolactin (PRL) production by human endometrial stromal cells in culture: Evidence for trophoblast-endometrial paracrine interaction. Presented at the 38th Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.

166. Levin JH, Tonetta SA and Lobo RA: Leuprolide acetate (LA) does not alter progestin stimulation of prolactin (PRL) production by human endometrial stromal cells in culture. Presented at the 38th Annual Meeting of the Pacific Coast Fertility Society, April 25-29, 1990, Scottsdale, Arizona.

167. Carmina E and Lobo RA: Serum levels of 5 androgen metabolites in hirsutism. Presented at the XXIII Congresso Della Societa Italiana di Endocrinologia, May 27-29, 1990, Porto Conte-Alghero, Italy.

168. Carmina E and Lobo RA: Effect of long term dexamethasone (DEX) or spironolactone (S) administration on clinical presentation and peripheral androgen metabolites in hirsutism. Presented at the 2nd European Congress of Endocrinology, July 1-6, 1990, Ljubljana, Yugoslavia.

169. Stanczyk FZ, Matteri RK and Lobo RA: An assessment of serum C_{19} sulfates and glucuronides as markers of peripheral androgen metabolism in women. Presented at the VIII International Congress on Hormonal Steroids, September 16-21, 1990, The Hague, The Netherlands.

170. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Norethindrone (NET) blocks the initial agonistic response to leuprolide acetate (LA). Presented at the 46th Annual Meeting of The American Fertility Society, October 13-18, 1990, Washington, D.C.

171. Ditkoff EC, Cassidenti DL, Paulson RJ, Sauer MV, Paul WL and Lobo RA: The GnRH antagonist, Nal-Glu, acutely blocks the LH surge but allows for resumption of folliculogenesis in normal women and in women undergoing hyperstimulation. Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991,

San Antonio, Texas.

172. Cassidenti DL, Sauer MV, Paulson RJ, Ditkoff EC and Lobo RA: A proposed protocol for the use of the GnRH-antagonist (Nal-Glu) in IVF cycles and its comparison to the GnRH-agonist (A). Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

173. Miles RA, Cassidenti DL, Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA: Percutaneous androstenedione as an in vivo test of inherent 5_{α}-reductase activity (5_{α}-RA). Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

174. Cassidenti DL, Stanczyk FZ and Lobo RA: The relationship between insulin resistance, IGF-1 levels, adrenal androgens and peripheral androgen metabolism in polycystic ovary syndrome (PCO). Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

175. Stanczyk FZ, Chang L, Carmina E and Lobo RA: Is 11β-hydroxyandrostenedione (11β-OHA) a better marker of adrenal androgen excess than dehydroepiandrosterone (DS)? Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

176. Levin JH, Stanczyk FZ, Vijod MA and Lobo RA: Growth factors stimulate prostaglandin production from human endometrial stromal cells in culture. Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

177. Chang L, Stanczyk FZ, Cassidenti DL, Putz Z and Lobo RA: Is the ovary a source of 11β-hydroxyandrostenedione among hyperandrogenic women? Presented at the 38th Annual Meeting of the Soc. for Gynecol Invest. March 20-23, 1991, San Antonio, Texas.

178 Presser SC, Stanczyk FZ, Delgado C and Lobo RA: Insulin sensitivity in postmenopausal women and the effects of estrogen. Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

179. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Factors affecting success of human in vitro fertilization (IVF) in unstimulated cycles. Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

180. Bergman A, Lobo R and Stanczyk FZ: Role of prostaglandins in detrusor instability. Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

181. Dodds WG, Friedman CI, Lobo R, Goldberg J and Kim MH: Low dose daily verses

alternate day dexamethasone therapy in adrenal hyperandrogenism. Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

182. Meme D, Shoupe D and Lobo R: Use of progesterone (P) releasing intrauterine device for protection of the endometrium in menopausal hormone replacement: A pilot study. Presented at the 38th Annual Meeting of the Society for Gynecologic Investigation, March 20-23, 1991, San Antonio, Texas.

183. Cassidenti DL, Paulson RJ, Lobo RA and Sauer MV: The synergistic effects of clomiphene citrate and human menopausal gonadotropins in folliculogenesis of hyperstimulated cycles as assessed by GnRH antagonist (Nal-Glu). Presented at the 39th Annual Meeting of the Pacific coast Fertility Society, April 10-14, 1991, Indian Wells, California.

184. Presser SC, Stanczyk FZ, Sauer MV, Delgado C and Lobo RA: Insulin induced stress responses and the effects of estrogen and progestin in postmenopausal women (PMW). Presented at the 39th Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, California.

185. Carmina E, Stanczyk FZ, Chang L, Miles RA and Lobo RA: The ratio of androstenedione (A)/11β-hydroxyandrostenedione (11β-A) is an important marker of adrenal androgen excess in women. Presented at the 39th Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, California.

186. Cassidenti DL, Matteri RK, Vijod AG and Lobo RA: Lack of correlation between the suppression of androgen levels and the ovulatory response in clomiphene resistant patients with polycystic ovary syndrome (PCO). Presented at the 39th Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, California.

187. Paulson RJ, Sauer MV, Francis MM, Macaso M and Lobo RA: Embryo implantation after in vitro fertilization (IVF) in unstimulated cycles. Presented at the 39th Annual Meeting of the Pacific Coast Fertility Society, April 10-14, 1991, Indian Wells, CA.

188. Ditkoff EC, Levin JH, Paul WL, and Lobo RA: Time-related fluorimmunoassay (FIA): A better clinical indication of LH biological activity. Presented at the 47th Annual Meeting of The American Fertility Society, October 19-24, 1991, Orlando, Florida.

189. Carmina E, Ditkoff EC, Vijod AG, Janni A and Lobo RA: Increased circulating levels of β-endorphin in PCO are not due to increased pituitary secretion. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

190. Millar LK, Goodwin TM, Stanczyk FZ, Lobo RA and Paul RH: Effect of 6 hour

infusion of the oxytocin antagonist atosiban on uterine activity and plasma PGFM. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

191. Ng S, Shoupe D and Lobo R: Peripheral vasodilatory effect of conjugated equine estrogens in postmenopausal women. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

192. Lindheim SR, Legro RS, Stanczyk FZ, Vijod MA and Lobo RA: Stress responses in pre- and postmenopausal women and the effects of estrogen. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

193. Ditkoff EC, Kornafel KL, Carmina E, Shoupe D, Stanczyk FZ and Lobo RA: Corticotropin-releasing factor decreases fasting insulin levels in patients with PCO. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

194. Carmina E, Getzschein E and Lobo RA: Evidence for increased androsterone metabolism in nonhyperandrogenic acne. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

195. Ditkoff EC, Fruzzetti F, Chang L, Stanczyk FZ and Lobo RA: Ovarian influence on adrenal androgen sensitivity and secretion in PCO. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

196. Price T, Carr B, Dupulis R, Stanczyk F and Lobo R: Multiple dose pharmacokinetics of a 35 μg ethinyl estradiol, 1 mg norethindrone oral contraceptive in women with chronic renal failure on peritoneal dialysis. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

197. Miles RA, Lobo RA, Paulson RJ and Sauer MV: The use of testolactone to prevent ovarian hyperstimulation syndrome (OHSS) after gonadotropin therapy. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio,Texas.

198. Carmina E, Koyma T, Chang L, Stanczyk FZ and Lobo RA: Ethnic variability in polycystic ovary syndrome (PCO): Insight into pathophysiology. Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

199. Paulson RJ, Sauer MV, Francis MM, Macaso TM and Lobo RA: Toward ultimate in vitro fertilization (IVF): Addition of the GnRH antagonist Nal-Glu and pure FSH to unstimulated IVF cycles, Presented at the 39th Annual Meeting of the Society for Gynecologic Investigation, March 18-21, 1992, San Antonio, Texas.

200. Miles RA, Lobo RA, Gentzchein E, Moyer D, Presser MF, Koopersmith T, Paulson RJ and Sauer MV: Assessing the pharmacodynamic properties of exogenously administered progesterone: A comparison of micronized vaginal delivery to intramuscular routes. Presented at the 40th Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.

201. Miles RA, Gentzschein E, Goedert L, Stanczyk FZ and Lobo RA: Assessment of androgen suppression using androstenedione gel. Presented at the 40th Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.

202. Lindheim SR, Ditkoff EC, Presser SC, Vijod MA, Stanczyk FZ and Lobo RA: A biomodal effect of estrogen on insulin resistance in postmenopausal women and a potential attenuating effect of progestin. Presented at the 40th Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.

203. Lindheim SR, Legro RS, Chang L, Vijod MA, Shoupe D, Stanczyk FZ and Lobo RA; Enhanced reactivity to induced behavioral stress in polycystic ovary syndrome. Presented at the 40th Annual Meeting of the Pacific Coast Fertility Society, April 8-12, 1992, Indian Wells, California.

204. Carmina E, Janni A and Lobo RA: Physiologic hormonal replacement enhances the effect of GnRH-agonist treatment for hirsutism in patients with ovarian hyperandrogenism. Presented at the 74th Annual Meeting of The Endocrine Society, June 24-27, 1992, San Antonio, Texas.

205. Stanczyk FZ, Carmina E, Gentzschein E and Lobo RA: Specific elevations in C19 conjugate levels in hyperandrogenic women with hirsutism. Presented at the 74th Annual Meeting of The Endocrine Society, June 24-27, 1992, San Antonio, Texas.

206. Cassidenti DL, Ary BA and Lobo RA: Leuprolide acetate (LA) followed by clomiphene citrate (CC) induces ovulation in clomiphene resistant patients with polycystic ovary syndrome (PCO). Presented at the 48th Annual Meeting of The American Fertility Society, October 31-November 5, 1992, New Orleans, Louisiana.

207. Lindheim SR, Legro RS, Vijod MA, Stanczyk FZ and Lobo RA: Does racial background influence the effect of estrogens on the hormonal response to stress? Presented at the 48th Annual Meeting of The American Fertility Society, October 31-November 5, 1992, New Orleans, Louisiana.

208. Lindheim SR, Kades WW, Wassilv VM, Chang L, Kojima T, Saad MF and Lobo RA: Effects of IGF-1 and insulin in PCO. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1991, Toronto, Ontario, Canada.

209. Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA: Substrate dependency of C19

conjugates in hyperandrogenic women and the influence of adrenal androgen. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

210. Lindheim SR, Sauer MV, Francis MM, Macaso TM, Lobo RA and Paulson RJ; Elevated early follicular phase FSH levels in unstimulated cycles: Effects on follicular dynamics and oocyte maturation. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

211. Duffy DM, Lobo RA, Paulson RJ and Sauer MV: Follicular and endometrial response to 3 fixed dose regimens of estrogen and progesterone among cycling women preparing for oocyte donation. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

212. Stanzcyk FZ, Gentzschein E, Kojima T, Ary BA, Ziogas A and Lobo RA: Comparison of urinary unconjugated progesterone with urinary pregnanediol glucuronide as a marker of luteal activity. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

213. Legro RS, Carmina E, Gentzschein E, Stanczyk FZ and Lobo RA: Evidence for decreased androgen glucuronidation in balding men and androgenic alopecia. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

214. Lindheim SR, Buchanan TA, Duffy DM, Vijod MA, Kojima T and Lobo RA: Estimates of insulin resistance in postmenopausal women: Comparison of the ITT and the IVGTT. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

215. Legro RS, Shahbarami B, Lobo RA and Kovacs B: Size polymorphisms of the androgen receptor among female Hispanics and correlation with peripheral hyperandrogenism. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

216. Legro RS, Muhleman D, Comings D, Lobo RA and Kovacs B: D3 receptor polymorphisms associated with oligo-ovulation among female Hispanics. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

217. Lindheim SR, Legro RS, Wong IL, Tran DQ, Chang L and Lobo RA: Attenuating effects of progestin on adaptation to behavioral stress in postmenopausal women. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-Aapril 3, 1993, Toronto, Ontario, Canada.

218. Wong IL, Chang L, Spahn M-A F, Lindheim SR, Stanczyk FZ and Lobo RA; Characterization of the ovarian steroidogenic abnormality in PCO. Presented at the 40th

Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

219. Legro RS, Blanche P, Krauss RM and Lobo RA: Alterations in atherogenic lipoproteins among hyperandrogenic women: Influence of insulin and genetic factors. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

220. Ary BA, Stanczyk FZ, Fahy MA and Lobo RA: 6-sulfatoxymelatonin levels in ovulatory women. Presented at the 40th Annual Meeting of the Society for Gynecologic Investigation, March 31-April 3, 1993, Toronto, Ontario, Canada.

221. Lindheim SR, Kojima T, Duffy DM, Vijod MA, Stanczyk FZ and Lobo RA: Insulin sensitivity is decreased in normal women by doses of ethinyl estradiol used in oral contraceptives. Presented at the 41st Annual Meeting of the Pacific Coast Fertility Society, April 14-18, 1993, Indian Wells, California.

222. Lindheim SR, Duffy DM, Kojima T, Vijod MA, Stanczyk FZ and Lobo RA: The route of administration influences the effect of estrogen on insulin sensitivity in postmenopausal women. Presented at the 41st Annual Meeting of the Pacific Coast Fertility Society, April 14-18, 1993, Indian Wells, California.

223. Lindheim SR, Sauer MV, Francis MM, Macaso TM, Lobo RA and Paulson RJ: In vitro fertilization (IVF) in unstimulated cycles: Utility of a midcycle FSH boost in addition to HCG for timing of follicle aspiration. Presented at the 41st Annual Meeting of the Pacific Coast Fertility Society, April 14-18, 1993, Indian Wells, California.

224. Carmina E and Lobo RA: Ovarian suppression reduces clinical and endocrine expression of late onset congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Presented at the 75th Annual Meeting of The Endocrine Society, June 9-12, 1993, Las Vegas, Nevada.

225. Morris RS, Carmina E, Vijod MA, Stanczyk FZ and Lobo RA: Alterations in the sensitivity of serum IGF-1 and IGF-BP3 to octreotide in polycystic ovary syndrome (PCO). Presented at the 75th Annual Meeting of The Endocrine Society, June 9-12, 1993, Las Vegas, Nevada.

226. Ary BA, Chang L, Gentzschein E, Vijod M, Stanczyk FZ and Lobo RA: Comparison of GRF and clonidine as probes for the GH axis in normal and clomiphene resistant women with PCO. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9-14, 1993, Montreal, Quebec, Canada.

227. Duffy DM, Lindheim SR, Ary BA, Saad M, Vijod MA, Chang L and Lobo RA: The effects of growth hormone releasing factor (GRF) and insulin-like growth factor-1 (IGF-

1) on folliculogenesis in normal women. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9-14, 1993, Montreal, Quebec, Canada.

228. Morris RS, Duffy DM, Lindheim SR, Gentzschein E, Spahn M-A, Chang L, Espinoza TB, Anderson PW and Lobo RA: Angiotensin converting enzyme (ACE) inhibition during the normal menstrual cycle. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9- 14, 1993, Montreal, Quebec, Canada.

229. Lindheim SR, Legro RS, Moris RS, Lobo RA, Paulson RJ and Sauer MV: Altered stress responses in women undergoing in vitro fertilization and in recipients of oocyte donation. Presented at the conjoint meeting of The American Fertility Society and The Canadian Fertility and Andrology Society, October 9-14, 1993, Montreal, Quebec, Canada.

230. Morris RS, Wong IL, Hatch IE, Paulson RJ and Lobo RA: Prorenin is elevated in PCO and may reflect hyperandrogenism. Presented at the 41st Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, Illinois.

231. Wilcox JG, Morris RS, Gentzschein E, Stanczyk FZ and Lobo RA; The biological effects of 17α-dihydroequilin sulfate and its possible modulation of hepatic production. Presented at the 41st Annual Meeting of the Society for Gynecologic Investigation, March 22-26, 1994, Chicago, and Illinois.

232. Wong IL, Morris RS, Chang L, Spahn MA, Stanzcyk FZ and Lobo RA: A prospective randomized trial comparing finasteride to spironolactone in the treatment of hirsute women. Presented at the 41st Annual Meeting of the Society for Gynecologic Investigation, March 22- 26, 1994, Chicago, Illinois.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S)	:	PICKAR, J., DEY M.
SERIAL NO.	:	09/808,878
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EXAMINER	:	M. Bahar

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND DECLARATION UNDER 37 C.F.R. § 1.132

SIR:

I, ROGERIO A. LOBO, M.D., declare as follows:

1. The statements made in my Declaration Under 37 C.F.R § 1.132 submitted on April 1, 2003 are incorporated herein, including information regarding my background and qualifications and my curriculum vitae attached as Exhibit A thereto.

2. For the past 20 years, the dosage of 0.625 mg CEE has been accepted as the minimum dosage of estrogen necessary to relieve the symptoms of menopause, including hot flushes and bone loss. (See, e.g., Sobel NB, Obstetrics and Gynecology Clinics of North America, 21:299-319 (1994) (describing 0.625 mg as the standard dose of conjugated estrogen) (Ex. A hereto); Kronenberg F, Chapter 9: Hot Flashes, in Rogerio A. Lobo, ed., Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, New York, NY: Raven Pres, at 109 (1994)) ("The most commonly used regimen for treating hot flashes in the United States is 0.625 to 1.25 mg of oral conjugated equine estrogen (Premarin)") (Ex. B hereto). The dosage of 2.5 mg of MPA has

been recognized as the minimum amount needed to oppose 0.625 mg CEE and protect the endometrium. This combination of 0.625 mg CEE plus 2.5 mg MPA daily has been the most commonly prescribed combination estrogen-progestin hormone replacement therapy regimen in the United States. (See, e.g., Kreling D, et al., Prescription Drug Trends: A Chartbook Update, Menlo Park, CA: Kaiser Family Foundation, at 51 (2000)) (Ex. C hereto).

3. The preferred dosage of CEE that Plunkett discloses is 0.600 mg CEE. Page 9 of Applicants' application compares the claimed invention to a combination using 0.625 mg CEE. The difference between the dosages of 0.600 mg CEE and 0.625 mg CEE is not a meaningful difference when compared to Applicants' invention. For purposes of treating or inhibiting vasomotor symptoms, one skilled in the art would consider a daily dosage of 0.600 mg CEE to be clinically equivalent to a dosage of 0.625 mg CEE. Therefore, Applicants provided comparative results of its claimed invention with the preferred dosages of MPA and CEE that Plunkett discloses.

4. The results on page 9 of Applicants' application describe some of the results obtained in the Women's Health, Osteoporosis, Progestin, Estrogen study ("H.O.P.E. study"). Relief of vasomotor symptoms was analyzed in patients who experienced at least an average of 7 to 8 moderate-to-severe hot flushes per day during the 7-day period just prior to the initiation of treatment in this study. The results on page 9 reflect the results of 4 of the 8 regimens used in the H.O.P.E. study administered daily: (1) 0.625 mg CEE plus 2.5 mg MPA ("PREMPRO"); (2) 0.45 mg CEE plus 1.5 mg MPA; (3) 0.3 mg CEE plus 1.5 mg MPA; and (4) a placebo. The first table on page 9 shows the mean number of hot flushes. The second table shows the mean daily severity of the flushes. These results are also shown in Figures 1 and 2.

5. The results on page 9 of Applicants' application show that all doses of CEE plus MPA reduced the mean number and mean severity of hot flushes experienced by the women in the clinical study compared with taking placebo. The mean daily number and mean severity of hot

flushes in the lower dosage groups were not significantly different than the mean number and mean severity of the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA. These results demonstrated that the combinations of 1.5 mg MPA with the lower doses, 0.45 or 0.30 mg, CEE, were as effective in rapidly reducing the number and severity of hot flushes to essentially the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

6. The results on page 9 of Applicants' application were contrary to what would have been expected to those skilled in the art. The results surprisingly and unexpectedly demonstrated that all doses of CEE and MPA reduced the number and severity of hot flushes experienced by the women in this study compared with women taking placebo. It was unexpected that providing a daily dosage of 1.5 mg MPA in combination with the lower doses, 0.45 or 0.30 mg, CEE, rapidly reduced the number and severity of hot flushes to the same extent as the much higher and commercially available dose combination containing 0.625 mg CEE and 2.5 mg MPA.

7. The H.O.P.E. study demonstrated that dosages of CEE and MPA may be better than equivalent dosages of unopposed CEE for vasomotor symptom relief. Previous studies with various dosages of CEE showed no additive effect of MPA on vasomotor relief. (See Greendale et al., Obstetrics and Gynecology, 92:982-988 (1998)). Greendale et al. reported studies using the following regimens: (1) placebo; (2) 0.625 mg CEE daily; (3) 0.625 mg CEE daily plus 2.5 mg MPA daily; (4) 0.625 mg CEE daily plus 10 mg MPA for 12 days per month; and (5) 0.625 mg CEE daily plus 200 mg micronized progesterone for 12 days per month. Greendale et al. reported that there was "convincing evidence" that regimens using CEE plus MPA were not more effective than CEE alone against vasomotor symptoms. However, the H.O.P.E. study unexpectedly demonstrated that at the particular low dose of 1.5 mg, MPA may contribute vasomotor relief in combination with the lower dosages of 0.3 or 0.45 mg CEE. These results are

preliminary evidence that there is a therapeutic role for MPA beyond endometrial protection when lower dosages of CEE are used. The H.O.P.E. study surprisingly demonstrated that at these low doses MPA may contribute to ameliorating the vasomotor symptoms.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the patent or any reexamination certificate issued therefor.

Dated: 12/15/03

ROGERIO A. LOBO, M.D.

OBSTETRICS AND GYNECOLOGY CLINICS OF NORTH AMERICA

Primary Care of the Mature Woman

VERONICA A. RAVNIKAR, MD, GUEST EDITOR

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PROGESTINS IN PREVENTIVE HORMONE THERAPY

Including Pharmacology of the New Progestins, Desogestrel, Norgestimate, and Gestodene: Are There Advantages?

Nancy B. Sobel, MD, PhD

HISTORY

The development and characterization of the synthetic progestins used in hormone replacement therapy (HRT) and contraception are an outgrowth of research on the hormonal control of reproduction conducted during the early to middle twentieth century. Progesterone was isolated from the corpus luteum of sows by Corner and Allen in the 1930s. Before this, progesterone had been synthesized commercially from plant (soy beans, yams) and animal (ox bile) sources. It was not until Marker successfully synthesized progesterone from the Mexican yam in the 1940s that large quantities of progesterone became available at a reasonable price. Natural steroids, however, are difficult to control. They are inactive when given orally and highly insoluble in plasma, and therefore, the search for orally active steroids was begun. Originally motivated by the synthesis of cortisone, chemists discovered the progestational activity of 19-norsteroids. In 1951, Djerassi[15] prepared a derivative of 19-nortosterone, norethisterone (known as norethindrone in the United States), which was the first highly effective, orally active progestogen for human use. In subsequent years, attention was focused principally on the potential of progestational agents to control abnormal bleeding, and then as a contraceptive agent, resulting in the first oral agent in the early 1960s.[17, 26, 82]

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PROGESTIN STRUCTURE AND NOMENCLATURE

Steroid hormones are derivatives of cholesterol, a 27-carbon compound, and have a common chemical structure based on the 4-ring perhydrocyclopentanephenanthrene molecule. This is composed of one 5-carbon and three 6-carbon rings lettered A through D and numbered counterclockwise (Fig. 1). The sex steroid hormones are divided into three main groups according to their number of carbon atoms: the 21 carbon (21C) pregnane nucleus, precursor for progestins (and corticoids); the 19C androgen series, based on the androstane nucleus; and 18C estrogen, from the estrane nucleus. Synthetic progestins are also classified into three groups: pregnanes, estranes, and gonanes.

Estranes and their derivatives, the gonanes, are employed predominantly in contraception, and all are derived from norethindrone. Because both groups are characterized by the absence of a methyl group between rings A and B (i.e., C19), they have been designated the 19-nortestosterone progestins or 19-norprogestins (Fig. 2). All the structures are similar, but the "minor" alterations in structure can lead to dramatic differences in biochemical activity. Estranes are characterized by the addition of an ethinyl group at position 17. Differences between estranes involve double-bond position (norethynodrel) and placement of acetate moieties (norethindrone acetate and ethynodiol diacetate). Norgestrel, the first gonane progestin, synthesized from norethindrone by Smith[61] in the early 1960s, is also included in this class.

The gonanes include norgestrel and its biologically active L-isomer, levonorgestrol (LNG). The gonanes are distinguished from the estranes by the addition of a methyl group at position C18 (Fig. 3). In the 1970s and 1980s, efforts were made to minimize the intrinsic androgenicity of the 19-norprogestins. This produced a new generation of progestins, the gonanes desogestrel (Organon, Org 2969), norgestimate (Ortho-Cilag, ORF 10131), and gestodene (Schering AG, SH T 546). Structurally, gestodene differs from LNG only by the presence of a double bond in the D ring between carbons 15 and 16. Desogestrel differs from these by the absence of a keto group at position 3. Norgestimate is LNG with an oxime group at C3 and an additional acetate group at C17.

Another group of progestins, the pregnanes, became available when it was discovered that acetylation of the 17-hydroxy group of 17-hydroxyprogesterone also produced oral potency. Pregnanes, C-21 progestins, are the class of progestins widely used for noncontraceptive applications such as HRT and the treatment of carcinoma. These include medroxyprogesterone acetate (MPA), megestrol acetate, chlormadione acetate, and cyproterone acetate. Each drug has substituents at the 17 and 6 positions. Interestingly, these agents were not used in oral contraceptives (OC) because early studies, later refuted, associated high doses with an increased incidence of carcinoma of the breast in beagle dogs. In fact, only one pregnane-containing OC, Provest, ever reached the US market.[17]

PHARMACODYNAMICS AND SELECTIVITY

On ingestion, oral steroids are absorbed by the small intestines. From there, they are transported by means of the portal system to the liver where they may be modified and circulated systemically or eliminated by biliary excretion. This is referred to as the liver's presystemic or *first-pass* effect. From the gallbladder, molecules are returned to the small bowel, reabsorbed into the portal circulation, or excreted in the feces.[63, 90] Norgestrel does not undergo a first-pass effect,[87] although most other progestins do, resulting in variations in bioavailability among users.

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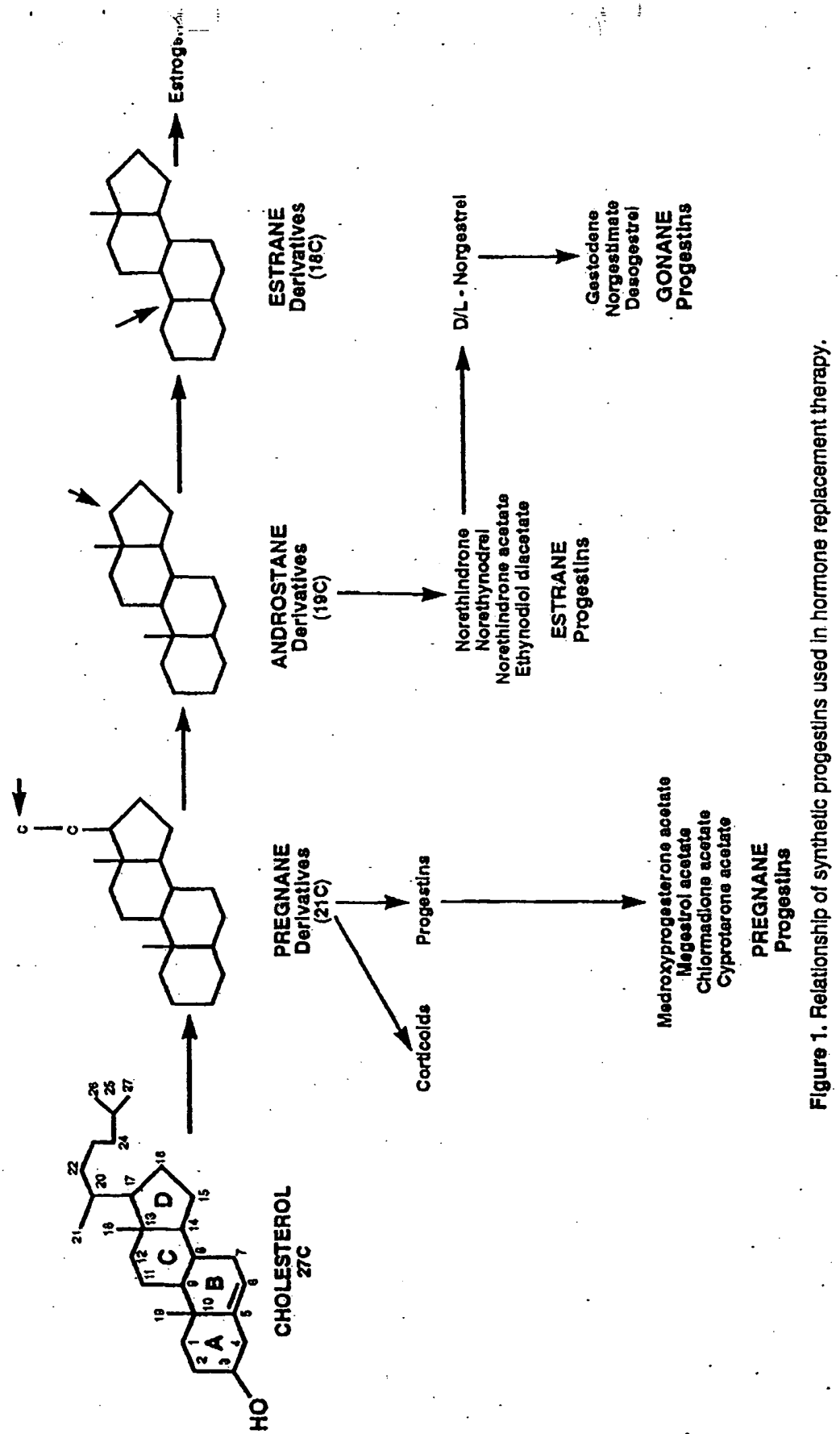

Figure 1. Relationship of synthetic progestins used in hormone replacement therapy.

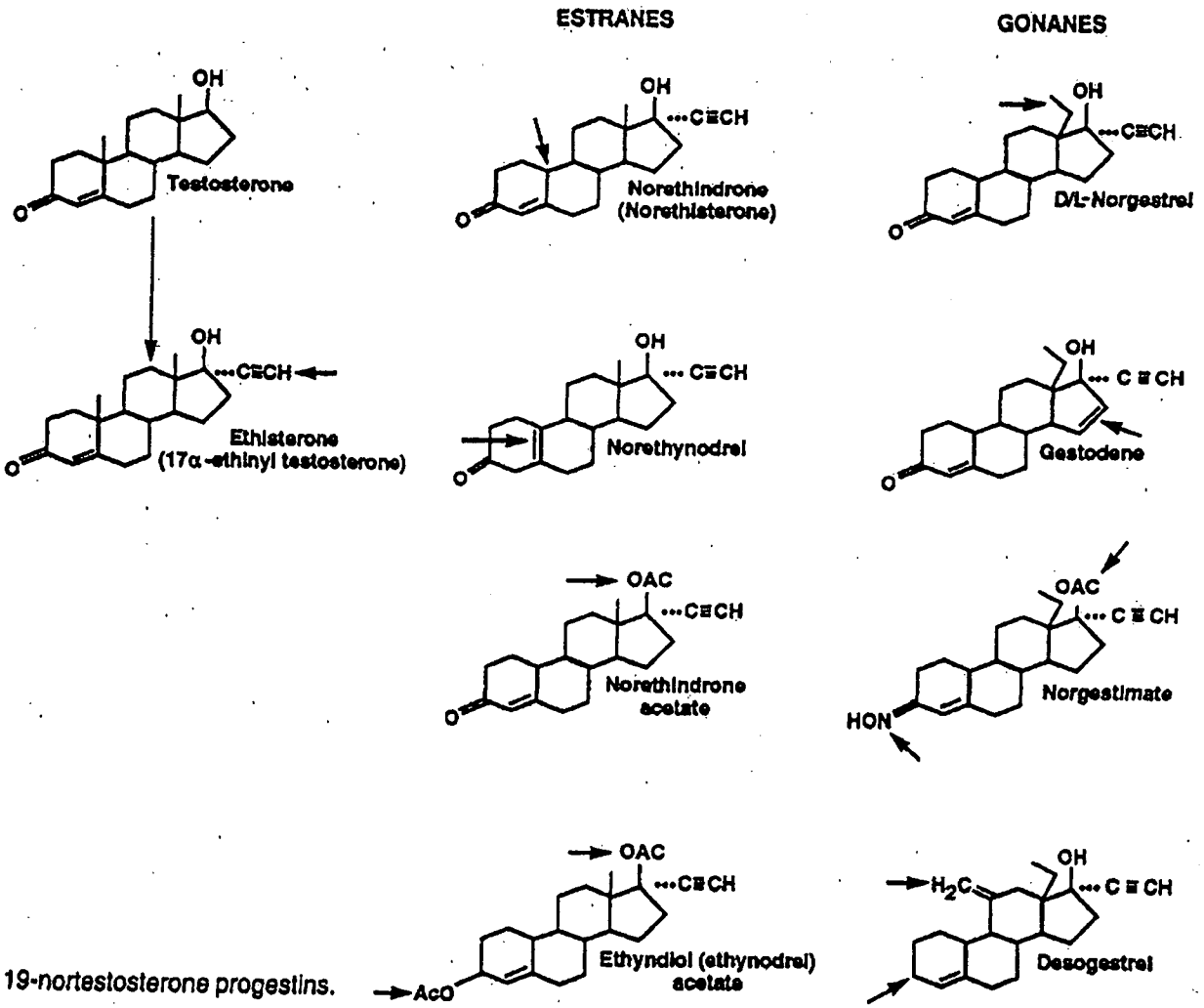

Figure 2. 19-nortestosterone progestins.

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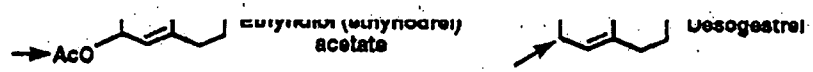

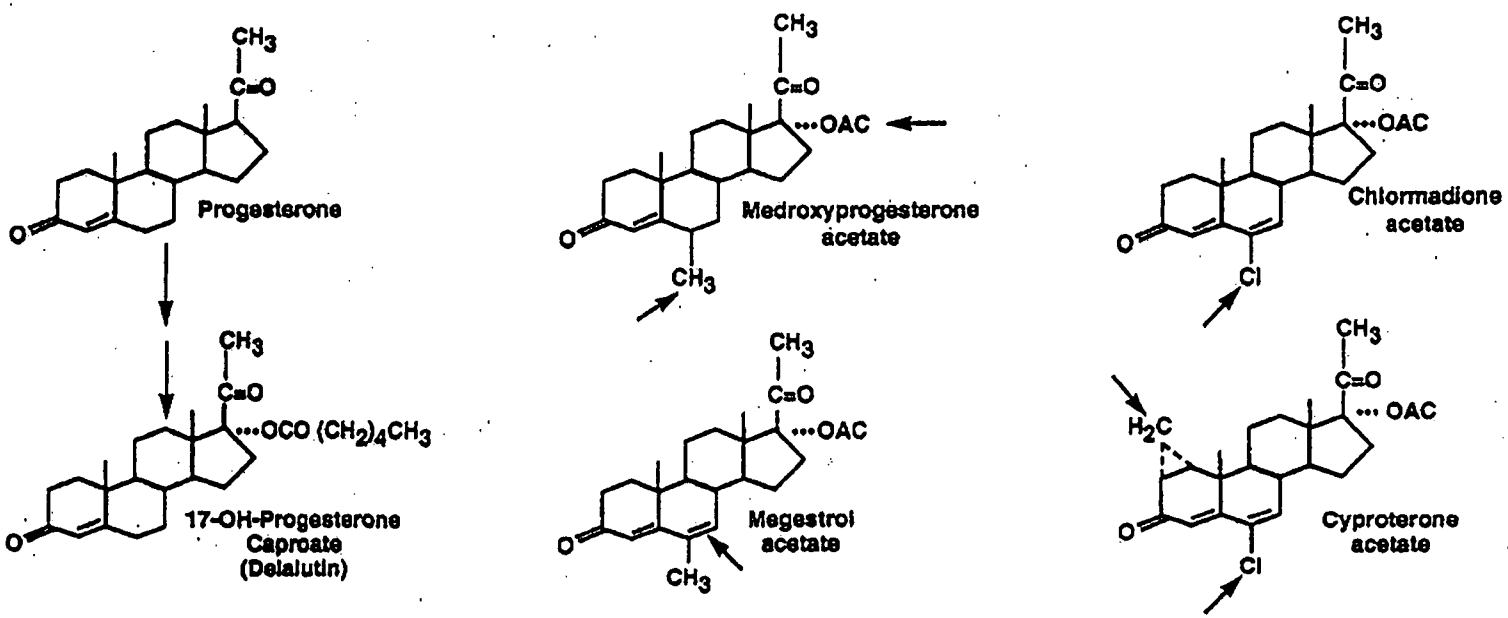

Figure 3. C-21 pregnane progestins.

Figure 4. *See legend on opposite page*

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Each progestin has a different affinity for sex hormone–binding globulin (SHBG) and can modulate the levels of SHBG, as can the estrogens with which they are used. The relationship between estrogen and progestin interactions has variously been described as the simple algebraic sum of their biologic activity (biogebraic),[96] and as a complex interaction between the effects of the estrogen and progestin components. These effects can result in the displacement of different amounts of free testosterone from SHBG, producing variable degrees of androgenicity. Several studies have shown different affinities of the new progestins for SHBG relative to LNG.

The half-lives of progestins range from about 10 hours (oral medroxyprogesterone acetate, megestrol acetate, norethindrone, and desogestrel) to more than 2 days (LNG and norgestimate). Use of compounds with a longer half-life may permit the suppression of gonadotropins during the 7-day placebo phase of the pill[90] and, by corollary, may help alleviate hot flushes when used in sequential HRT. The intramuscular form of MPA, Depo-Provera, has an elimination half-life of about 50 days.

Estranes are converted to norethindrone, although not completely, and thus formulations that use these compounds may lower progestin potency and side effects.[90] Norethynodrel has been noted to have some estrogenic activity on endometrium. Although some investigators believe that this is the result of traces of mestranol left over from the synthetic process, other authors[46] have demonstrated that all the estranes have weak binding to the estrogen receptor protein. Norgestrel exists as a 50:50 racemic mixture, the D-form of which is biologically inactive. Its purified form is levonorgestrel; thus, at any dose, LNG has twice the potency of D/L-norgestrel.

The new gonane progestins, all derivatives of norgestrel, have been used in Europe for more than a decade and were recently introduced into the United States. Desogestrel is converted in two steps into its active metabolite 3-ketodesogestrel[34] (11-methylene LNG). Norgestimate is biologically active as are its metabolites 17-deacetylnorgestimate, D-norgestrel, levonorgestrel, and 3-ketonorgestimate.[60] Gestodene has the highest progestogenic activity of the newer compounds as well as a marked affinity for the aldosterone receptor protein.[18] Oral contraceptive formulations using desogestrel are now the most prescribed in Europe. To date, no United States formulation contains gestodene.

In 1988, following a published assertion[47] that ethinyl estradiol (EE) levels appeared elevated among women using gestodene-containing formulations, an apparent increase in thromboembolism was noted in anecdotal reports of complications to the German government. No increase in phlebitis, however, has been demonstrated clinically with the use of any OC containing the new progestins, gestodene and desogestrel.[44] No association with thrombophlebitis was found in controlled clinical trials with estrogen replacement therapy.[5]

Based on the compilation of data[14, 18, 52, 67, 93] by Dickey,[13] the activities of different oral progestins in animal assays with respect to progestagenic and androgenic effects are shown in Figure 4. In these pharmacologic studies, as well as in many others, gestodene is the most powerful progestin. Gonanes, other than norgestimate, have higher progestagenic activity than estranes in receptor-binding and bioassays (see Fig. 4). Unfortunately, the C18 methylation of the

Figure 4. See legend on opposite page

Figure 4. Biologic activity of selected progestins. Oral activity in different animal assays: black bar = progestin activity, shaded bar = androgen activity. (*Data from* references 13, 14, 18, 52, 67, and 93.)

gonanes accorded increased progestogenic potency but also enhanced the androgenic activity of the molecule.[52] Norethynodrel, as well as the pregnanes, are without androgenic activity in the studies of Phillips,[67] on which Figure 4 is based; although Bergink[3] indicated that the pregnanes, particularly MPA, have small but measurable binding to androgen receptors.

Figure 5 represents progestagenic selectivity calculated from the same compilation of data used in Figure 4. Selectivity is the ratio between the desired and undesired pharmacologic effects, in this case the ratio of progesterone-mediated effects to those of androgen. In theory, this means that, at the therapeutic dose used, the drug has a far greater effect on the system intended to be manipulated than on other systems. Although, using these data, desogestrel is the most selective of the synthetic progestins studied and is marketed by its manufacturer as such, ethynodiol diacetate, the progestin in the OC Demulen is equally selective, although one tenth as potent by weight. Several in vitro receptor-binding preparations show similar trends. Other data from Phillips et al[67] suggested that norgestimate is the most specific of the three new progestins. Kloosterboer,[52] using a different progestin as the reference compound, showed gestodene to be the most selective. It should be cautioned, however, that these results are based on bioassays in different species and tissues (from rabbit endometrium to rat ventral prostate) and, in effect, are evaluating data from "apples and oranges." In addition, activities of the parent compounds, not their active metabolites, were used. Receptor-binding and bioassay data may not extrapolate to humans. Discrepancies may well exist among biochemical, animal, human biologic activity, and clinical spectrum. For example, if all estranes are metabolized to norethindrone, it would be anticipated that they would have identical profiles in vivo. Variables influencing biochemical assays include choice of tissue and species, intact versus fractionated cells, and other incubation conditions. Overall effect may vary by dose, formulation, and combination with estrogen. Currently, it is too early to evaluate whether enhanced selectivity will translate into decreased risk of serious sequelae. No study to date has shown any clinical significance of enhanced selectivity.

CLINICAL EFFECTS

Although progestins are the primary active compound in OCs, estrogen being present for cycle control, progestins play a secondary but important role in HRT. They were added to prevent changes that had been noted with unopposed estrogen administration, allaying the major fear of endometrial carcinoma, which may prevent patients from using HRT.

Steroid hormones are known to affect a myriad of systems. This review concentrates on the benefits for which HRT is most commonly prescribed, endometrial protection, cardiovascular disease, osteoporosis, and vasomotor flushes, and briefly reviews one controversial area, the possible effect on carcinoma of the breast. A comprehensive literature review[29] regarding the risks and benefits and effect on life expectancy of HRT as well as clinical guidelines of the American College of Physicians[30] have recently been published.

Effects on Endometrium

Retrospective studies[80, 106] published in 1975 showed an increase in endometrial hyperplasia and carcinoma in women treated with estrogen alone, which, in most patients, may be prevented by the addition of a progestational agent. The

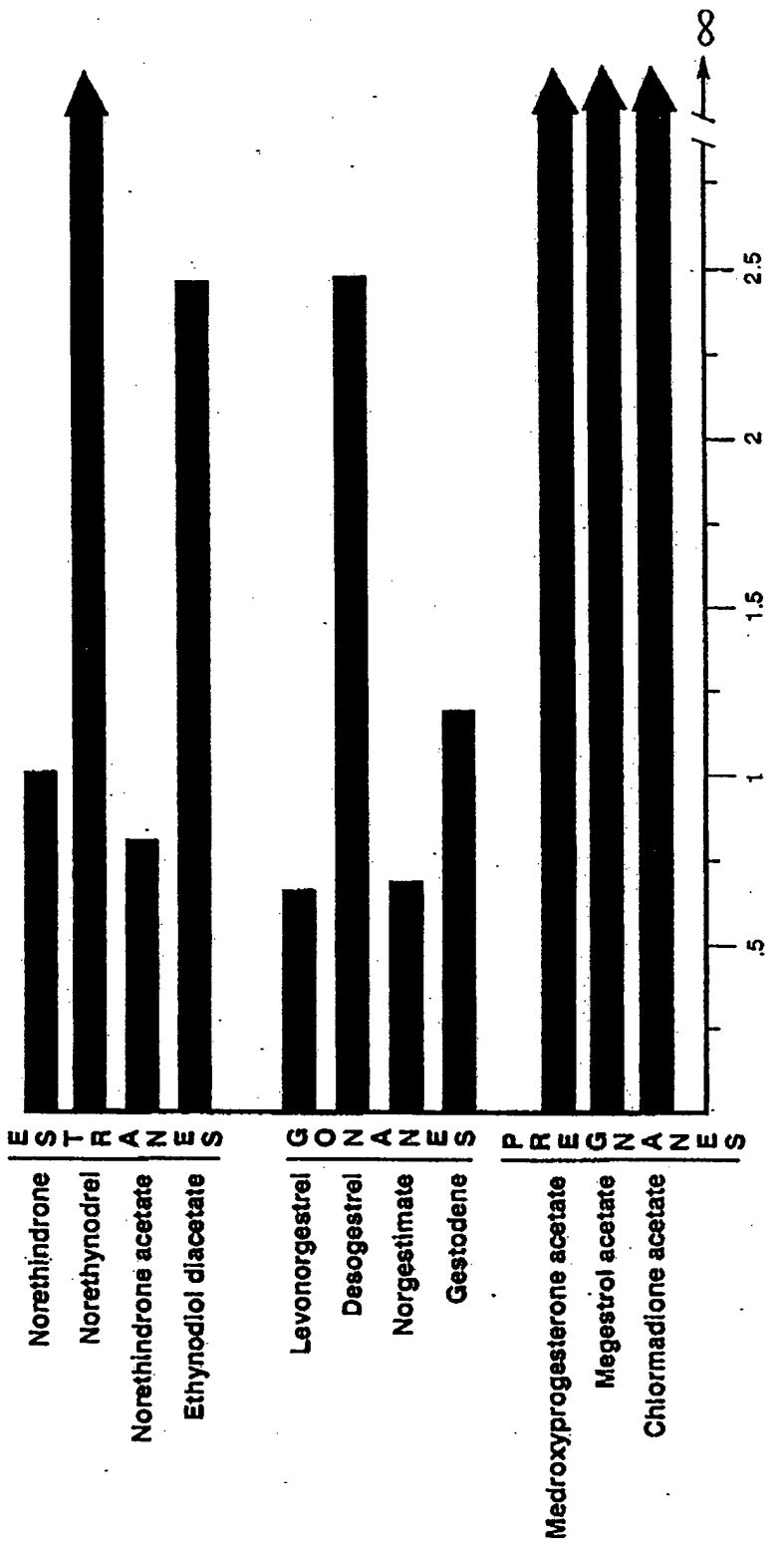

Figure 5. Selectivity of progestin. Ratio of progestin to androgen activity of oral steroids in animal assays. (*Data from* references 13, 14, 18, 52, 67, and 93.)

addition of progestin, as in combined estrogen-progestin therapy, can actually lower the incidence of the development of endometrial hyperplasia[102] and carcinoma.[25] In a 5-year prospective study with 4-year follow-up results, Gambrell et al[25] reported that the incidence of endometrial carcinoma was significantly decreased from 248 out of 100,000 women in the general population to 56 out of 100,000 women, figures that are lower than those in the control group without therapy, thereby making the use of HRT a form of prophylaxis compared with women who do not use HRT. Varma[97] reported that the addition of a progestin for more than 10 days monthly resulted in no evidence of cystic hyperplasia in 392 women. Other authors[7, 25] demonstrated that the addition of a progestin decreased the rate of hyperplasia from more than 20% without progestins to less than 1% if progestins were added for 12 or 13 days. Over time, doses of progestin used in HRT have been decreased without adverse effects on the endometrium. A limit to the beneficial effect has been demonstrated histologically and biochemically at higher doses of norethindrone and norgestrel,[103] possibly because of decreasing levels of estrogen-induced progesterone receptors or enzymes.

Cardiovascular Disease, Lipids, and Lipoproteins

It is predicted that almost 60 million persons, 20% of the US population, will be more than 65 years old in the year 2025. Cardiovascular diseases account for the deaths of over half a million women annually in the United States; more than 50% of these deaths are the result of ischemic heart disease. Dozens of studies have demonstrated an apparent relationship between serum lipoproteins and heart disease. Many of these studies, however, have been performed only in men with the results extrapolated to women, which is unacceptable. Although not all authorities agree that the death rates from arterial disease increase after menopause, other than the increase from premature surgical oophorectomy,[11] a number of studies of different designs, including tens of thousands of women, have shown an apparent 50% to 70% decrease in the risk from coronary heart disease in women taking oral estrogen.[2, 37, 84, 85, 86]

The first observational reports of the benefit of estrogen replacement therapy appeared in two sequential articles in the October 1985 volume of the *New England Journal of Medicine*, presenting data from the Nurses' Health[86] and Framingham studies.[104] The latter study initially proposed an increased risk; however, reanalysis of the data showed a 50% protection against coronary artery disease, bringing the conclusions in line with many other studies published to date.[16] Similar results have been documented more recently with combined (estrogen and progesterone) HRT.[22, 62, 94] Several mechanisms have been postulated to mediate this beneficial impact. These include direct effects on endothelial elements in vessels; secretion of vasoactive peptides leading to vasodilation; a balance between thrombotic and atherogenic mechanisms[71]; and changes in carbohydrate, prostacyclin, or lipoprotein metabolism.[29] Lipid changes seen with HRT may be a benefit of pharmacologic doses rather than being a physiologic effect of "replacing" missing hormones.

The Lipid Research Clinic study[6] concluded that about 30% of cardiovascular risk is due to lipoproteins. Much of the data to date related to the effect of progestins on the cardiovascular system have investigated the impact of lipids and lipoprotein mechanisms.

Lipoproteins are high–molecular weight proteins that transport lipids through the plasma. The polar lipids form a core, predominantly triglycerides in very low-density lipoprotein (VLDL) and cholesterol ester in high-density lipo-

protein (HDL) and low-density lipoprotein (LDL). This core is surrounded by a surface coat of hydrophilic phospholipids, including apoproteins (A-I and A-II in HDL and B-100 in LDL) that help to maintain particle solubility and to direct the lipoproteins to their site of metabolism by binding to cell membrane receptors. During the process that begins with intestinal chylomicron formation, proportionally more triglyceride is removed leaving a higher concentration of cholesterol. In order of increasing density, this leaves VLDL, LDL, and HDL, HDL_3, HDL_{2a}, and HDL_{2b}. Normally as triglycerides are removed, remnants (intermediate-density lipoproteins [IDL]) and LDLs are returned to the liver and taken up by hepatic receptors. Multiple factors, including increased dietary fat, may result in excess levels of circulating remnants in the plasma. Oxidation of IDL and LDL is thought to result in the accumulation of lipids in arterial wall macrophages, initiating atherosclerosis. High-density lipoprotein is thought to play a role in "reverse cholesterol transport" of lipids from cells to the liver for excretion. High-density lipoprotein appears to provide a protective effect,[28] and LDL correlates with an increased risk of heart disease. Estrogens, in general, are thought to increase HDL, triglycerides, and apoprotein B and to lower LDL, partially by decreasing levels of the enzyme hepatic lipase. Walsh et al,[98] in a study using oral estrogens, reported a 15% increase in HDL, a 16% decrease in LDL, and no appreciable advantage of doubling doses except on triglycerides after 3 months. A dose of transdermal estrogen, 0.05 mg, was shown to have no appreciable effect on HDL at 6 weeks,[98] but a significant effect was noted at 24 weeks with the 0.1 mg transdermal patch.[88] Some studies[39, 91, 95] showed the most dramatic effect on women with elevated cholesterol levels or coronary artery disease. The Leisure World study[37] looked at the effect of estrogens on women with previous myocardial infarction or cerebrovascular accident and reported a 50% decrease in risk of dying from subsequent myocardial infarction or cerebrovascular accident. Sullivan[91] evaluated women angiographically and noted that women with the worst coronary artery disease had a better 10-year survival than those not taking estrogen.

Estrogens and progestins, however, sometimes have opposing effects. Early studies[21, 39, 40, 64, 94] suggested that some progestins, particularly the "older" 19-norprogestins, may detrimentally affect cardiovascular risk by lowering HDL and triglycerides and elevating LDL, thereby potentially reversing some of the beneficial effects of estrogen. These studies, however, were often of short duration, small sample size, and used high doses of progestin (10 mg MPA or norethindrone acetate [NETA]). For example, the often-quoted Hirvonen[39] paper had only six patients in each of three study arms. Comparisons of natural progesterone with synthetic progestagens in sequential regimens demonstrated decreased levels of HDL with the synthetic progestagens but no adverse influence of natural progesterone on the beneficial changes in lipids from estrogen,[33, 43, 64] except that HDL was decreased with the 300 mg dose of progesterone.[21] Part of the discrepancies may be caused by the different assays used to measure lipoprotein levels. Estimation of levels of lipoproteins can be influenced by the expertise of the laboratory staff and the biochemical and mathematic techniques employed. For example, the Friedewald[23] formula, which is often used to calculate LDL and VLDL from total cholesterol and HDL, may give different values than when these are estimated using centrifugal density gradients.

Some longer-term studies[97] have shown that these short-term effects on lipids may be reversed over time, possibly because of the induction of enzymes. Since the late 1980s, reports of combined HRT have shown decreases in LDL and total cholesterol levels with modest changes in HDL over 1- to 5-year periods. In some instances, the change in HDL parallels that in estrogen only or placebo controls, and both tend to return to baseline levels after 1 year.[9, 12, 42, 43, 99] With continuous therapy over 5 years using estradiol 2 mg, NETA 1 mg, or a placebo,

Table 1. SUMMARY OF EFFECTS OF PROGESTINS ON LIPOPROTEINS USING COMBINED OR SEQUENTIAL HORMONE REPLACEMENT THERAPY FOR MORE THAN 6 MONTHS

Agent	Dose (mg)	Sequential or Combined	HDL	LDL	TG	TC
Estrogen only			↑	NS/↓	↑	NS
Progestin						
NETA	0.25–1.0	Both	NS/↓	↓	NS	↓
TTS-NETA	0.25	Sequential	NS	↓	↓	↓
		Combined	NS	NS	NS	NS
D/L-NG	0.075–0.5	Sequential	NS/↓	↓	NS/↓	↓
	0.25	Combined	↓	↓	↓	↓
LNG	0.075	Sequential	NS	↓	—	—
MPA	10	Sequential	NS/↓	NS/↓	NS	↓
	5	Both	↑/NS	NS/↓	↑/NS	NS/↓
	2.5	Combined	↑/NS	NS/↓	NS	NS/↓
CPA	1.0	Sequential	NS	↓	NS	↓
Megace	7.5	Sequential	NS	↓	↓	↓
	5	Combined	NS	↓	NS	↓
	2.5	Combined	NS	NS	↑	NS
Micr Prog	200	Both	↑/NS	↓	NS	NS/↓
DSG	0.15	Sequential	↑/NS	↓	NS/↓	NS/↓
		Combined	↓	↓	↓	↓

CPA = cyproterone acetate; D/L-NG = D/L-norgestrel; DSG = desogestrel; HDL = high density lipoproteins; LDL = low density lipoproteins; LNG = levonorgestrel; Micr Prog = micronized progesterone; MPA = medroxyprogesterone acetate; NET = norethindrone; NETA = norethindrone acetate; NS = not significant; TC = total cholesterol; TG = triglycerides; TTS-NET = transdermal norethindrone; ↑ = significant increase; ↓ = significant decrease.

total cholesterol and LDL each were reduced 20% in the HRT group, triglycerides were unchanged, and HDL was reduced in both the treated and control groups.[8]

Table 1 is a summary of available data regarding the effect of combined* and sequential† HRT for greater than 6 months on lipoprotein levels. Other than one report of opposing effects on triglycerides,[12] little difference is seen between oral or transdermal forms of progestin, using either low-dose 19-norprogestins or C-21 pregnane progestins, including MPA, megestrol and cyproterone acetate. Note that the 2.5 and 5 mg doses of MPA, 200 mg dose of micronized progesterone, and the 0.15 mg sequential dose of desogestrel have effects similar to those seen with unopposed estrogen. This may be the result of the lower doses used rather than the specific progestins. However, the decrease in HDL and triglycerides, as well as LDL and total cholesterol, with 0.15 mg of desogestrel in combined HRT[57a] does not support this theory. Cyclic variations continue to be seen in HDL and apo A-I levels between the estrogen only and estrogen-progesterone phases in combined-sequential HRT; these were exaggerated in smokers.[32]

Many researchers and clinicians believe that the new progestins may have important advantages over those now in use, such as fewer changes in lipid metabolism, thereby potentially diminishing the risk of cardiovascular problems. At the present time, no US studies have appeared, and few foreign studies use the new progestins in HRT. Published reports currently are limited to desogestrel. Foreign studies, in general, have few controls and compare fixed HRT combinations in which both estrogens and progestins differ between study arms.

*References 8, 9, 33, 42, 57, 57a, 59, 70, 83, 99, 105, 107.
†References 2, 21, 33, 39, 41, 43, 55, 57, 58, 66, 69, 70, 74, 78, 92, 105.

The majority used sequential regimens of estrogen and MPA 5 mg, NETA 1 mg, LNG 75 μg, or desogestrel 150 μg for 10 days per month and reported significant decreases in LDL and minor or cyclic changes in HDL.[31, 58] Only a report from Israel[92] showed an advantage with the new progestin, desogestrel, compared with sequential doses of MPA and NETA. Over a 9-month period, HDL was calculated to increase 30% with desogestrel, 20% with MPA, and not significantly with NETA. However, NETA was used at a 1-mg dose in combination with estradiol and estriol, whereas conjugated equine estrogens were matched with different durations of desogestrel and MPA use. Low-density lipoprotein decreases were 10% (MPA), 15% (NETA), and 27% (desogestrel). To date, no direct comparison has been made of the effectiveness of the three new progestins other than in OCs in which desogestrel, norgestimate, and gestodene appear to increase triglyceride levels and have no significant effect on LDL or total cholesterol.[73] A recent review[48] shows desogestrel having different effects on lipoproteins when used in OCs increasing HDL and triglycerides and having no significant change in LDL level; one might speculate that these differences are caused by the greater proportion of estrogen in OCs.

Many studies, particularly with continuous HRT, show a decrease in LDL and total cholesterol over time. Three studies,[32, 59, 83] however, demonstrated no significant change in HDL/LDL or total cholesterol/LDL ratios with combined-continuous HRT. Even if both HDL and LDL are reduced, a beneficial effect may occur when the reduction of LDL is greater than that of HDL. Conversely, if studies show the beneficial effect persists in the presence of lipoprotein levels returning to baseline levels, this may imply indirect support of some of the other hypotheses mentioned previously. In addition, it is not yet known whether a statistically significant change in levels will also be clinically significant. A recent observational study has documented that HRT is associated with such a favorable physiologic profile,[62] but further randomized trials are required. The ongoing Women's Health Initiative[11a] may help to answer this question.

Osteoporosis

Osteoporosis affects 15 to 20 million women—half to one third of postmenopausal women. It is estimated to result in 1.3 million fractures annually and to cost 7 to 10 billion dollars a year in the United States. Peak cortical bone density occurs in women at 35 years of age, whereas trabecular density occurs somewhat earlier and decreases rapidly 3 to 7 years after menopause, about 15% every 10 years. Bone mass is affected by a number of additional variables, including age, genetics, calcium, medications, activity, smoking, and coexisting medical conditions.

Absorption of calcium in the gastrointestinal tract appears to be compromised in menopausal women and improved by estrogen replacement. An increase in oral calcium intake, however, is not enough.[72] Estrogen has been documented to increase absorption of calcium in the gastrointestinal tract, decrease bone resorption, and retard postmenopausal bone loss.[27, 36] Estrogen may prevent up to 80% of vertebral compression fractures and 50% to 60% of fractures of the hip and arm. No data are available relating to the effect of estrogen on death rate from hip fracture. A recent report,[22a] however, indicated that at least 7 years of estrogen therapy after menopause are needed for long-term protection of bone mineral density, and even this may not protect women aged 75 years and older.

There is evidence[9, 69] that combined estrogen and progestin therapy prevents postmenopausal bone loss, possibly uncoupling of bone formation and resorp-

tion.[10] Others[19, 43, 57, 58, 76, 89] have shown that various combinations of estrogen and progestins, including the transdermal form of progestins, may lead to increased bone formation. Lee[53] hypothesized that progesterone, not estrogen, is the missing factor in the prevention and treatment of osteoporosis. A few studies[35, 58, 74] (although again of questionable, suboptimal design) that compared desogestrel with the older progestins demonstrated reversal of indexes of bone resorption, decreased bone turnover, and prevention of bone loss. More work is needed to clarify the relationship between the effect of estrogen and progesterone and whether any benefit will be derived from use of the new progestins.

Vasomotor Flushes

Vasomotor flushes ("hot flashes") occur in 85% to 90% of menopausal and postmenopausal women and are the reason many women seek medical assistance during the climacteric. Estrogen has been shown to decrease or eliminate hot flushes. In a randomized, double-blind crossover study, Campbell and Whitehead[7] using estrogen 1.25 mg, showed that hot flushes were substantially reduced and sleep was increased. Schiff et al,[75] using a sleep unit, noted a decrease in sleep latency and an increase in REM sleep during estrogen therapy. Progesterone, however, has also been shown to alleviate vasomotor flushes. In women in whom estrogen but not progestin therapy is contraindicated, two progestins have been found to be efficacious in decreasing or relieving hot flushes: MPA, 10 to 40 mg/day or Depo-Provera, in 1- to 3-month intervals as needed; and megestrol acetate (Megace), 20 to 80 mg/day. Unfortunately, progestins do not provide the beneficial effects of estrogen on genital tissues, and some women experience vaginal dryness and resultant dyspareunia with these medications. No work to date has been published regarding the new progestins and vasomotor flushes. Other, nonsteroidal, methods for relief of flushes have been reviewed by Miller.[61]

Carcinoma of the Breast and Hormone Replacement Therapy

Many women fear carcinoma of the breast far more than heart disease or osteoporosis, although the risk of death from cardiovascular disease is about 10 times greater. Some women decline the use of HRT and hormonal contraception despite the lack of current data clearly demonstrating that estrogens or progestins affect the risk of developing breast carcinoma, a risk that increases linearly with age in all women. A variety of studies have been performed to try to elucidate the relationship between sex steroids and carcinoma of the breast. For many years, it was assumed that the breast, like the endometrium, would respond to progesterone stimulation with a protective effect. But biochemical differences in response to progesterone stimulation have been demonstrated[102] between these two tissues. To date, more than 40 studies in the English literature have investigated the question of HRT with and without progestins and breast carcinoma without a clear consensus. Data from Gambrell et al[24] appear to document a protective effect of progesterone with respect to cancer. Two Scandinavian reports[4, 20] suggest the converse. Several large studies show no increased risk. Therefore, until such a positive relationship is more clearly documented, many authorities[39, 100] recommend using estrogen-only HRT in women who have undergone hysterectomy in view of the potential detrimental effects of progestins on cardiovascular risk.

DOSE RECOMMENDATIONS

Hormone replacement therapy currently is prescribed both sequentially and continuously. The classic sequential method attempts to simulate the hormone pattern of premenopausal women and produces a secretory endometrium. Most regimens combine 10 to 14 days of a progestin with 25 days of estrogen per month, although no additional risk of endometrial hyperplasia was demonstrated by combining daily estrogen with cyclic MPA.[33] Using endometrial biopsies, Padwick and colleagues[65] documented that a 5-mg dose of progesterone may be used safely. Women who bleed before day 10 of progestin administration often require a higher dose in subsequent cycles to produce full conversion to a secretory endometrium.[65] Unfortunately, a large number of women experience withdrawal bleeding well into their 60s with the sequential combination.

Recently, the so-called continuous-combined method that involves a constant daily dose of both estrogen and progestin has come into vogue. Its primary advantages include the use of a lower daily dose of progestin, which potentially results in fewer adverse metabolic changes and side effects; these include the dysphoric effects on mood[77] noted with some preparations, as well as breast tenderness, bloating, and headache. In addition, these regimens eventually produce amenorrhea from an atrophic endometrium. On the negative side, however, up to 80% of women experience breakthrough bleeding in the first 6 months and 10% at 12 months. The bleeding in both this and the classic sequential HRT method often results in a major problem with compliance.

Standard estrogen doses, with both sequential and combined regimens, include conjugated (0.625 mg), micronized (1 to 2 mg), or transdermal (0.05 mg) estrogen. In many instances, current doses of progestin in HRT are similar to those in OC preparations. Although equivalent potencies of oral progestins on estrogen-primed endometrium were shown by King and Whitehead[50] to be 5 mg of medroxyprogesterone, 0.35 mg norethindrone, 0.075 mg of D/L-norgestrel, and 200 mg micronized progesterone, the standard dosages of progestins in the sequential regimens usually are 5 to 10 mg of medroxyprogesterone acetate (Provera, Cycrin, Amen), 0.075 mg D/L-norgestrel (Ovrette), 2.5 to 5 mg norethindrone (Micronor, Norlutin, NorQD), 5 to 10 mg norethindrone acetate (Norlutate, Aygestin), 150 μg desogestrel, or 200 mg of micronized oral progesterone daily for 10 to 14 days. Daily continuous combinations usually involve MPA 2.5 to 5 mg, norethindrone 0.35 to 2.1 mg, norethindrone acetate 1 mg, or desogestrel 150 μg/day. Alternate treatments include 250 μg/day of levonorgestrel (Norplant) or Depo-Provera every second or third month to decrease withdrawal bleeding. The longer-term effects on endometrium with these regimens are not yet clear. All of the new progestins are dosed lower than most other commonly used progestins. As mentioned previously, desogestrel has been used at 150 μg daily in both continuous and sequential regimens. Norgestimate has been used effectively in European OCs at daily doses as low as 250 μg and gestodene at 75 μg. Studies being conducted with considerably lower doses may show them to be equally efficacious in HRT with lowered effects on lipids. When it is necessary to use unopposed estrogen, endometrial sampling has been recommended annually or when the endometrial stripe becomes greater than 4 to 8 mm on transvaginal ultrasonography.[54] Archer et al[1] have reported that pretreatment biopsy is unjustified in asymptomatic women with a less than 0.75% yield of cancer or atypia.

ON THE HORIZON

To improve convenience and compliance, many parenteral combinations of steroids have been postulated, some of which are being tested. These include

injectable suspensions and microspheres, transdermal patches combining estrogen and progestagens,[49,55,56,102] subdermal implants, such as the Norplant system, and some biodegradable varieties of implants and pellets. Vaginal rings, when investigated for contraceptive use, produced satisfactory blood levels of hormones.[91] Use of progesterone intrauterine devices, which release 65 mg progesterone daily,[79] have been described for the prevention of endometrial hyperplasia in postmenopausal women.

CONCLUSION

The first hormonal contraceptive combination, introduced in 1960, contained mestranol 150 μg, and norethynodrel 10 mg. Both contraceptive and hormone replacement doses have dropped more than 90% in the intervening years. The current ratio of progestin to estrogen dose in OCs by weight covers a range of more than tenfold, from less than 5 to 50. The biologic activity of the estrogens in OCs, now predominantly ethenyl estradiol, has been shown to be many times that of the estrogens used in HRT. Accordingly, the potential exists for progestin doses in HRT to be decreased even further in the future with the possibility of additional reduction in adverse effects. It is too early to see whether the new progestins will offer any clinical advantages over older compounds. Current data do not uniformly support this concept. Conversely, an optimal combination of estrogen and progestins for prevention of osteoporosis has not yet been determined, nor has a consensus been reached about the effect of steroid hormones on carcinoma of the breast. Therefore, the optimal regimen and route of HRT await the results of future studies.

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Treatment of the Postmenopausal Woman

Basic and Clinical Aspects

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CHAPTER 9

Hot Flashes

Fredi Kronenberg

Hot flashes are the classic sign of menopause as well as the predominant complaint of perimenopausal and menopausal women in the United States, yet it was not until 1975 that serious scientific study of hot flashes was undertaken. In that year, a paper on the measurement of physiological changes during hot flashes demonstrated their objective existence (1), and the phenomenon could no longer be dismissed as being "all in the head," as it often had been previously.

A hot flash is a sudden, transient sensation ranging from warmth to intense heat that spreads over the body, particularly on the chest, face, and head, typically accompanied by flushing, perspiration, and often followed by a chill. In some instances, there are palpitations and a feeling of anxiety. Although these are characteristic features of a hot flash that make it an identifiable phenomenon, the magnitude and duration of any of these components can vary both within and among individuals, and not everyone experiences all of them. So some women flush, others do not; some sweat profusely, others hardly at all. Descriptions of hot flashes may also include pressure in the head or chest, a burning sensation, nausea, feelings of suffocation, and the inability to concentrate. Thus, just as the 28-day menstrual cycle is seen more in textbooks than in women, women's experiences of hot flashes are more variable than most textbook definitions.

Whether referred to as hot flashes, hot flushes, night sweats, or vasomotor symptoms (terms that are often used interchangeably), these episodic events can disrupt women's sense of well-being and can create problems for professional and social life.

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EPIDEMIOLOGY

Hot flashes primarily affect women who are in the transition to menopause or have become menopausal, whether naturally or due to medical intervention such as ovariectomy, chemotherapy, radiation, or medications that cause estrogen levels to fall. At other stages of the female reproductive life cycle, however, some women describe symptoms very similar to the hot flashes of menopause. A small percentage of premenopausal women report having hot flashes, as do women during pregnancy or in the early postpartum period.

Hot flashes may also be experienced by men upon abrupt loss of testicular function such as occurs following orchiectomy for prostatic or testicular cancer, following certain surgical procedures that compromise testicular function (2–5), or upon administration of GnRH agonists, which result in a fall in testosterone levels (6,7). Men who are hypogonadal due to other causes also can experience hot flashes (4).

Until relatively recently, most of the epidemiological studies of menopause had been conducted in North America and Europe (8–13). These studies found that the majority of women had at least some hot flashes. The prevalence of hot flashes is highest in the first two postmenopausal years, ranging from 58% to 93% in these studies, and lessens over time. In perimenopausal women, reports of hot flash prevalence range from 28% to 65%, and in premenopausal women, from 6% to 63%. Women with surgically induced menopause, at least for the first year postovariectomy, tend to have a relatively high prevalence of hot flashes, comparable to that of women in the first two years of natural menopause (see Tables 1 and 2 of ref. 14 for details of specific studies).

Hot flashes, although frequently occurring with menopause, are not universally experienced. Studies of menopause are now underway in countries around the world, and the data available thus far suggest that

the high prevalence of hot flashes in Western societies is not the experience everywhere. Hot flashes have been reported in many cultures, including Indian, African, Native American, Japanese, Indonesian, Mexican American, Mayan, Thai, Filipino, and Chinese (15–24). But the prevalence of hot flashes within these cultures varies widely. Thus far, the most extensively studied non-Western group has been Japanese women, who report very few hot flashes (18,25). Mayan women in Yucatan, Mexico, do not report any symptoms at menopause other than menstrual cycle irregularity (21). These studies raise interesting questions. Are the physiological changes that are so characteristic of hot flashes in American women truly absent in other groups? Are they present but perceived differently? Are they, perhaps, not attributed to menopause? If absent or experienced by only a small percentage of the population, could this be due to diet, exercise patterns, or other cultural differences? Current research efforts may soon provide answers to some of these questions, and the results may generate leads to new methods of treatment. Increasingly, the patients in a medical practice come from a wide variety of cultural and religious backgrounds. It is therefore necessary to be aware of the menopausal symptoms that may be seen among women of other cultures, as well as to be sensitive to various cultural and medical traditions that might preclude a particular approach to treatment of hot flashes or include treatments not used by Western physicians.

NATURAL HISTORY OF HOT FLASHES

The initial form of hot flashes and their pattern over time differ among women, but the physiological basis for these differences in hot flash patterns and presentations has yet to be definitively explained. For some women, hot flashes begin as menstrual cycles are becoming irregular: they tend to occur when menstrual cycles are absent and disappear when menstrual cycles resume. For others, hot flashes begin when menstrual cycles are still regular, which may be well before menopause. There are also instances in which hot flashes first begin several years after menopause (14). Few investigators have asked about the age and menstrual cycle status at which hot flashes begin, but those who have asked report that for a majority of women hot flashes begin prior to menopause (12,14,26).

The frequency, intensity, and duration of individual hot flash episodes vary both within and among individuals. Hot flashes may occur once a month or as often as every half hour. Most women with hot flashes have them infrequently, but about 10% to 15% of women have very frequent, severe hot flashes (14). Women with frequent hot flashes often have relatively consistent patterns of hot flashes, at least in the short-term. Over months or years, however, an individual's hot flash pattern may change. In many cases hot flashes first occur at night and eventually occur during the day as well. Generally, hot flashes tend to become less frequent over time; however, for some women, they continue at frequent intervals until well into old age (14,27). The intensity of hot flashes can range from mild to very intense, over the course of one day, from day to day, or in different seasons. An individual hot flash episode typically lasts 3 to 6 min, although it can be of shorter duration, and on occasion a hot flash can last for more than 30 min.

The period of time over which hot flashes are most often experienced is 6 months to 2 years; however, women can have hot flashes for 10, 20, or even 40 years (14,26,28). Adequate data on the natural course of hot flashes is lacking because most investigators have not asked women across the life cycle whether they are having hot flashes. Most often excluded are women in their seventies and eighties; it had been assumed, incorrectly, that they would no longer have been experiencing hot flashes.

Although hot flashes often occur spontaneously with no observable trigger (particularly during sleep), some women report specific precipitating factors for their hot flashes. Psychological stress is often cited, as are hot weather (particularly hot, humid weather), a confining space, caffeine, alcohol, and spicy foods (14,29,30).

Few studies have examined factors that might predispose women to hot flashes. No significant association has been found between the occurrence of hot flashes and sociodemographic variables such as employment status, social class, age, or marital status (13). Women with hot flashes are not distinguishable from those without hot flashes by age at menarche, number of pregnancies, or previous medical problems (31). One factor that has been shown to relate to the occurrence of hot flashes in menopausal women is mean body weight and percent ideal body weight. Asymptomatic women had significantly higher mean body weight, percent ideal body, and total circulating estrogen levels, than women with hot flashes (32). Recent data from a prospective study of the natural menopausal transition indicate that women with longer perimenopausal periods were more likely to report hot flashes than were those with a short perimenopausal period (51% as compared with 39%) (33). Further research will determine whether factors such as genetics, diet, and exercise will be found to influence hot flashes.

PHYSIOLOGY OF HOT FLASHES

Thermoregulatory and cardiovascular changes that accompany a hot flash are now well documented.

Characteristic patterns exist amid a range of individual variability (Fig. 1, Table 1). Knowledge of the time sequence of physiological changes during a hot flash has grown incrementally as researchers have measured additional parameters. It is now frequently reported that many women have a premonition of an impending hot flash (an aura), which they distinguish from the hot flash itself. This prodromal feeling is often described as one of disease, anxiety, a tingling sensation, or pressure in the head (14). During this period immediately prior to the onset of a hot flash (approximately 5 to 60 sec), heart rate and cutaneous blood flow begin to increase (34,35).

At the start of a hot flash typically there is a sudden onset of sweating primarily on the upper body but measurable all over the body, as indicated by a rapid drop in skin resistance (increase in skin conductance) (35,36). The main sensation is one of intense heat, although internal body temperature never rises above normal. As cutaneous blood flow increases (34,35) and heart rate continues to accelerate (4 to 35 beats/min) (34,35,37), skin temperature rises, particularly that of the fingers and toes (1 to 7°C) (1,35,38,39), and sweating continues. Evaporative cooling may cause the temperature of the wet skin to drop, particularly on the chest and forehead, where sweating tends to be profuse (35). Heart rate and skin blood flow peak within about 3 min of hot flash onset (34,35). To relieve their discomfort, women initiate a variety of behavioral measures to dissipate heat. The vasodilation, sweating, and behavioral responses result in heat loss and a drop in internal temperature (0.1 to 0.9°C), which reaches a nadir about 5 to 9 min after the onset of the hot flash (35,36). If there has been significant heat loss and core temperature has dropped, there may be the sensation of a chill, or even some shivering as the hot flash resolves. Vasoconstriction, behavior to promote warming, and at times an increase in metabolic rate due to shivering, facilitate the return of body temperature to normal. Skin temperature gradually declines to its pre-hot-flash level. This can take 30 min or more, depending on skin and ambient temperatures. No change in blood pressure has been found in association with a hot flash (34,37,40). Although sweating and the

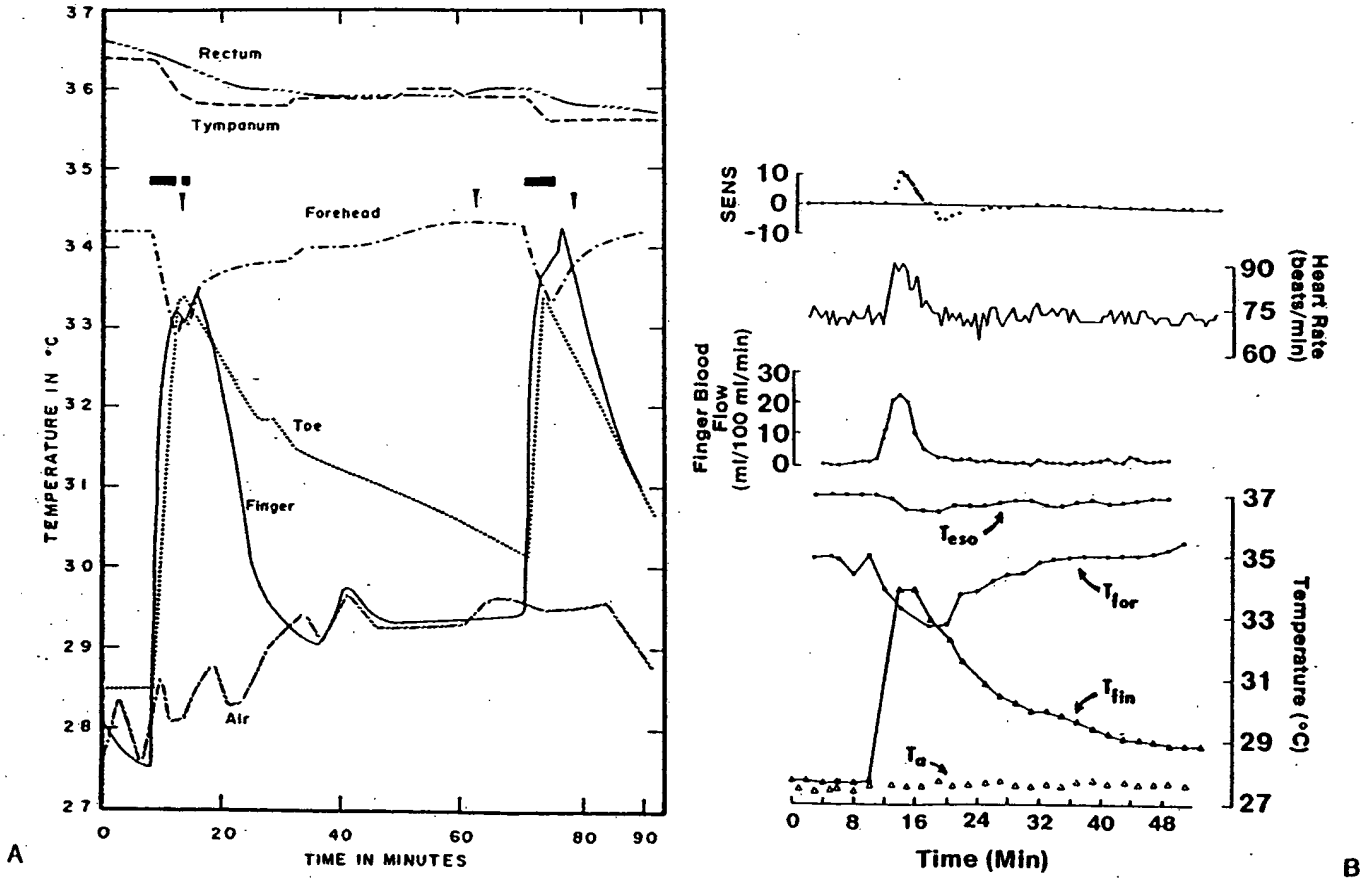

FIG. 1. A: Temperature responses to two spontaneous flashes (▪) and evoked flash (■). ↓, Finger stab for blood sample. Nude. (From ref. 1, with permission.) B: Thermoregulatory and cardiovascular changes during a typical hot flash at an ambient temperature of 28°C. Subjective sensation, blood flow (finger), heart rate (30-sec averages), skin resistance (chest), internal body temperature (vagina), and skin temperatures (forehead, finger) are depicted. (From ref. 14, with permission.)

TABLE 1. *Clinical picture of a hot flash*

Symptom	Description
Sensation	Sudden feeling of heat and sometimes anxiety
Heart rate	Increases (5–35 bpm), sometimes felt as palpitations
Cutaneous blood flow	Increases; observed as flushing
Finger skin temperature	Rises rapidly (1–7°C) and slowly declines after hot flash ends
Sweating	Often profuse, with rapid onset; rate of evaporation depends on ambient humidity and temperature
Core temperature	Decreases (0.1–0.9°C) several minutes after hot flash starts; sometimes felt as a chill at end of hot flash
Sleeping problems	Increase in nighttime awakenings associated with hot flashes (night sweats)

perception of heat are most intense on the upper body, the temperature of the toes increases concomitantly with finger temperature, and sweating may occur over the lower body as well (1,35), demonstrating that a hot flash is a generalized physiological phenomenon.

The subjective perception of the intensity of a hot flash is likely due to a combination of factors, including the associated sweating and increased heart rate, and probably involves other ill-defined sensations. The sensation of hot flash intensity is not a direct function of absolute skin temperature or the change in skin temperature during a hot flash, since the degree to which finger skin temperature increases during a hot flash is inversely proportional to the baseline skin temperature before the hot flash (Fig. 2) (35,36,41). The more distal the site, the lower skin temperature is likely to be initially and, therefore, the greater the potential for seeing an appreciable rise in skin temperature during a hot flash. As a result, in many studies finger temperature is used as an objective indication of a hot flash. This measurement works well in cool ambient temperature, but less well in warm ambient temperatures when baseline skin temperature already may be high.

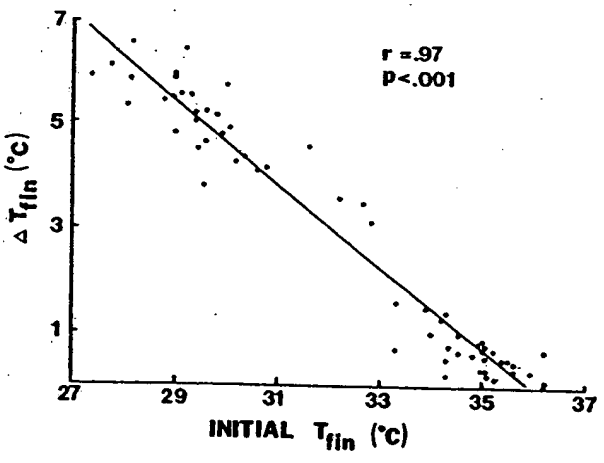

FIG. 2. Relationship between the maximum increase in finger temperature (T_{fin}) during a hot flash and the finger temperature immediately before the hot flash (INITIAL T_{fin}). (From ref. 85, with permission.)

ENDOCRINOLOGY OF HOT FLASHES

Estrogen

Given the long-known association of hot flashes with the onset of menopause and of menopause with a drop in circulating levels of estrogen, investigators have sought to determine whether there might be a relationship between estrogen and hot flashes. In early studies, no correlation was found between estrogen levels in the blood and the presence or absence of hot flashes in postmenopausal women (42–45), nor were any acute changes in estradiol or estrone associated with individual hot flashes (46). In other studies, postmenopausal women with severe hot flashes were found to have lower levels of circulating estrone and estradiol than did asymptomatic women (Fig. 3) (32,47,48). More specifically, Erlik et al. (32) found the fraction of estradiol not bound to sex hormone-binding globulin (SHBG) to be significantly higher in asymptomatic women than in women with hot flashes. Although estrogen does not appear to trigger individual hot flashes, levels of plasma estrogens do play some, as yet undetermined, role in the etiology of hot flashes.

Hot flashes involve more than just the presence of low plasma estrogen levels. Throughout the postmenopausal period, estrogen levels remain low, yet some women never have hot flashes, while for others, hot flashes may occur only sporadically or may soon cease. In other situations in which estrogen levels are low, such as in prepubertal girls or women with anorexia nervosa, hot flashes are not reported. Furthermore, hot flash-like episodes are reported during pregnancy (particularly the last trimester), when plasma estrogen level becomes particularly high (F. Kronenberg, *unpublished data*). Hot flashes also occur in premenopausal women during pituitary suppression with a gonadotropin-releasing hormone (GnRH) agonist, when serum estradiol concentration is maintained at premenopausal levels (49).

What seems to be more important than levels of es-

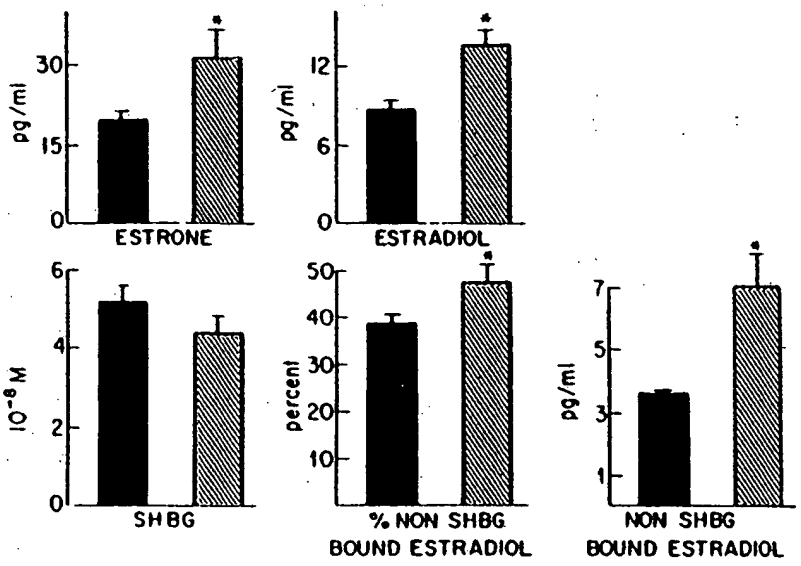

FIG. 3. Mean ± SE levels of estrone, estradiol, sex hormone-binding globulin (SHBG), percent non-SHBG-bound estradiol, and non-SHBG-bound estradiol in 24 women with hot flashes (*solid bars*) compared with 24 asymptomatic subjects (*striped bars*). Asterisk indicates significantly different from asymptomatic subjects. (From ref. 32, with permission.)

trogen per se is a drop in estrogen concentration. For example, the abrupt onset of hot flashes following ovariectomy (42,50) or the administration of GnRH analogues, which cause plasma estrogen to fall (51,52), support this contention. So does the observation that postmenopausal women with gonadal dysgenesis (Turner's syndrome) who have never had normal adult estrogen levels do not experience hot flashes unless they are first prescribed, and then withdrawn from, estrogen (38,53). Estrogen therapy generally ameliorates hot flashes, and upon discontinuation of estrogen treatment, they often return. There have been no reports to indicate whether women with hot flashes have a more precipitous natural decline in estrogen than do those who never have hot flashes.

Hot flashes have also been reported by men upon acute withdrawal of testosterone, such as after total orchiectomy (2,3). The decline in testosterone as men age is far more gradual than the decline in estrogen that occurs in women, which may be the reason that hot flashes are not frequently reported in men. Thus a sudden decrease in sex steroids in either women or men can precipitate hot flashes.

The specific role of estrogen in the etiology of hot flashes remains to be fully understood. In addition to its effect on reproductive tissues, estrogen influences thermoregulatory, neural, and vascular functioning. The firing rate of thermosensitive neurons in the preoptic area of the hypothalamus in response to thermal stimuli can be modulated by estrogen (54). Estrogen also influences internal body temperature, although the direction of the effect differs between studies (55,56). The responsiveness of vascular smooth muscle to vasoactive substances such as epinephrine and norepinephrine is affected by estrogen (57) and has been shown to be greater in women with hot flashes than those without hot flashes (58). Thus estrogen may have peripheral as well as central effects that are important to hot flash physiology.

Luteinizing Hormone (LH)

In addition to the study of estrogen's relationship to hot flashes, the role of gonadotropins has been examined as well, since gonadotropin levels become elevated at menopause. However, high gonadotropin levels are not the direct cause of hot flashes, since (a) LH level remains high postmenopausally while hot flashes tend to lessen, (b) no differences in absolute levels of LH have been found between women with and without hot flashes (59), and (c) hot flashes can be diminished by estrogen doses insufficient to reduce LH levels in the blood (60). Furthermore, when anti-gonadotropins such as danazol or GnRH analogues are given to women with endometriosis, hot flashes often occur despite a decline in LH level (60).

Thus absolute LH level has provided little insight into hot flash etiology. When serial blood samples were drawn, however, LH in the peripheral circulation was found to exhibit a temporal correlation with hot flashes (Fig. 4); most hot flashes are accompanied by an increase in LH (38,39). The correspondence of LH pulses with hot flashes led to speculation that LH might be responsible for the initiation of hot flashes. But it was soon evident that a pulse of LH was not a necessary concomitant of hot flashes. Hot flashes can occur in women who have no episodic LH release such as those with hypophysectomy (Fig. 5) (61,62), in pre- or postmenopausal women in whom pulsatile LH release has been suppressed by treatment with a GnRH agonist (Fig. 6) (51,63,64), and in women with pituitary insufficiency and hypoestrogenism (62). Ravnikar et al. (65) found there to be a similar number of LH

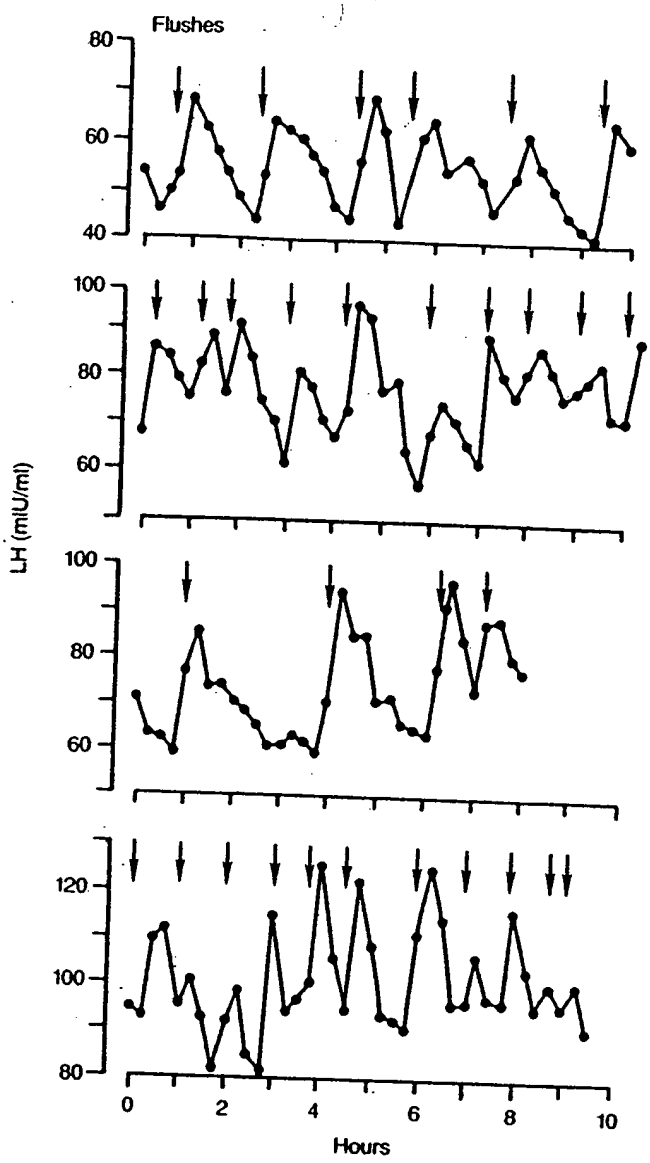

FIG. 4. Pattern of pulsatile LH release and associated menopausal flush episodes. *Arrows* indicate flush onset. Each part illustrates a separate 8- to 10-hr study in which blood samples were obtained at 15-min intervals. Note that each flush is synchronized with an LH pulse. (From ref. 38, with permission.)

pulses in women with or without hot flashes. Thus LH secretion per se is not the immediate trigger of hot flashes.

Gonadotropin-Releasing Hormone (GnRH)

Since pulses of LH were not directly responsible for initiating hot flashes, but they were associated with hot flashes, it was thought that perhaps hot flashes might be initiated at the hypothalamic level and involve the releasing factor for LH. Immunoreactive GnRH was measured in the peripheral circulation of women with and without hot flashes and discovered to be elevated prior to the LH pulses observed with hot flashes. Women with hot flashes also had higher mean plasma immunoreactive GnRH levels than did asymptomatic women (65). Yet women with defects in GnRH synthesis or release (isolated gonadotropin deficiency), who received estrogen treatment, had hot flashes when they were withdrawn from estrogen (66). Furthermore, when GnRH receptors were blocked with a long-acting GnRH antagonist in women who never had hot flashes, although LH pulses were abolished, these women experienced hot flashes for the first time (51). Thus episodic GnRH release is not necessary for hot flashes to occur.

Other Endocrine Studies

Circulating epinephrine and norepinephrine have been measured during hot flashes by several investigators with conflicting results. Casper et al. (38) found no change in epinephrine or norepinephrine in association with individual hot flashes. Given the 2- to-3-min half-life of epinephrine and norepinephrine (67), Kronenberg et al. (35) sampled at more frequent intervals and found a significant increase in plasma epinephrine and a decrease in norepinephrine during hot flashes (Fig. 7). Mashchak et al. (68) found epinephrine to increase but saw no change in norepinephrine levels.

Other substances that have been measured in the peripheral circulation during hot flashes are listed in Table 2. Circulating β-endorphin, β-lipotropin, and adrenocorticotropic hormone (ACTH) increase in association with hot flashes (Fig. 8) (69,70), as do cortisol, dehydroepiandrosterone (DHEA), and androstenedione (46,69,70) (Fig. 9). The peak levels of most of these substances are reached after the subjective hot flash has ended. Prolactin level did not change during hot flashes. Once again, no causal relationships have been found.

HOT FLASHES AND SLEEP

One of the primary complaints of women with hot flashes is that their sleep is disrupted. They may awaken several times during the night, drenched in sweat, necessitating a change of bedding and clothes. Erlik and co-workers (71) used electroencephalography (EEG) to demonstrate that nocturnal awakenings in postmenopausal women with hot flashes were correlated with the occurrence of the hot flashes (Fig. 10). Sleep efficiency is lower and latency to REM (rapid eye movement) sleep is longer in women with hot flashes compared to those with no hot flashes (72). This disturbed sleep often leads to fatigue and irritability during the day. The frequency of awakenings and

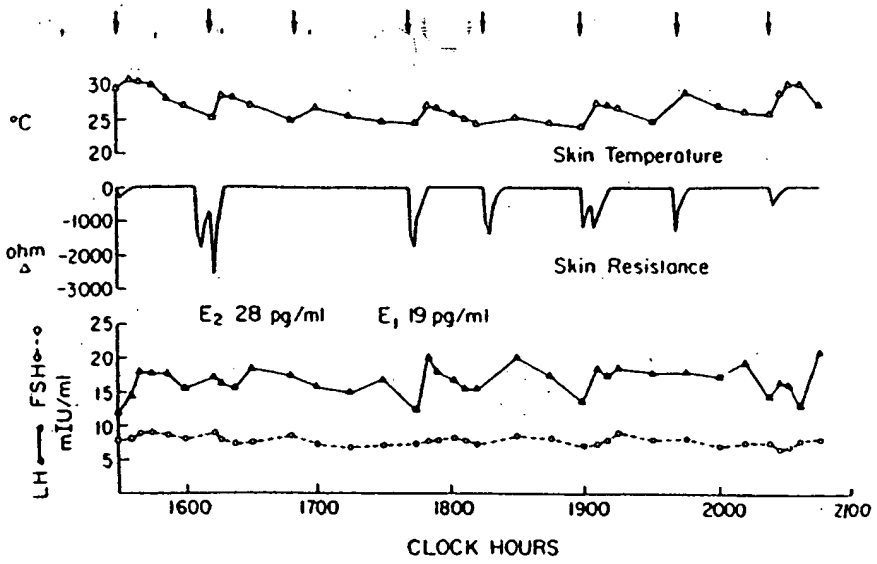

FIG. 5. Serial measurements of skin temperature, skin resistance, and serum LH and FSH levels in a woman after hypophysectomy (patient 1). Skin resistance changes are depicted at 1-min intervals as the change in ohms from the baseline immediately preceding the episode. *Arrows* mark the onsets of subjective hot flushes. E_2, estradiol; E_1, estrone. (From ref. 62, with permission.)

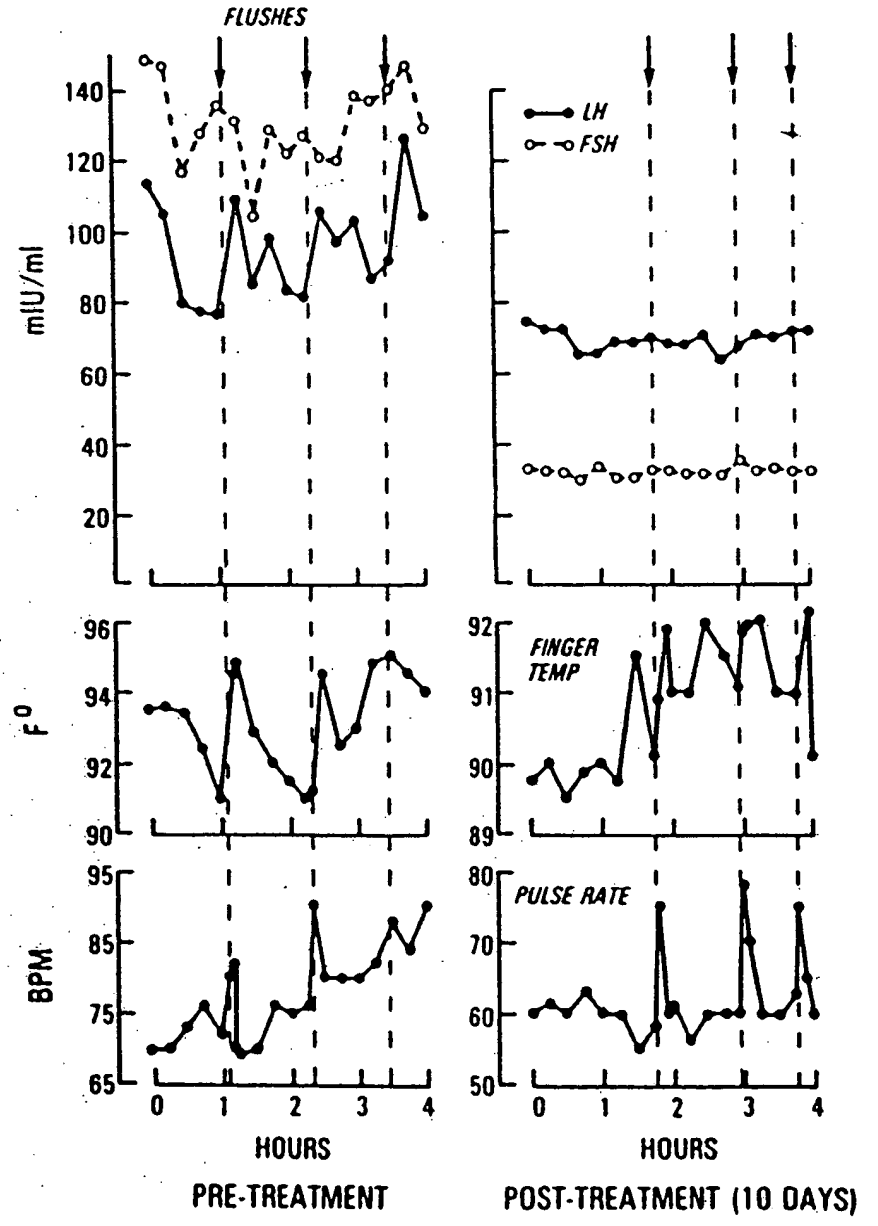

FIG. 6. Changes in finger temperature (°F) and pulse rate (beats/min) in association with flush episodes (*arrows*) and serum concentrations of LH (●–●) and FSH (○–○) in a representative study of one hypogonadal subject before and after 10 days of daily LRF-Ag administration (50 μg sc). (From ref. 63, with permission.)

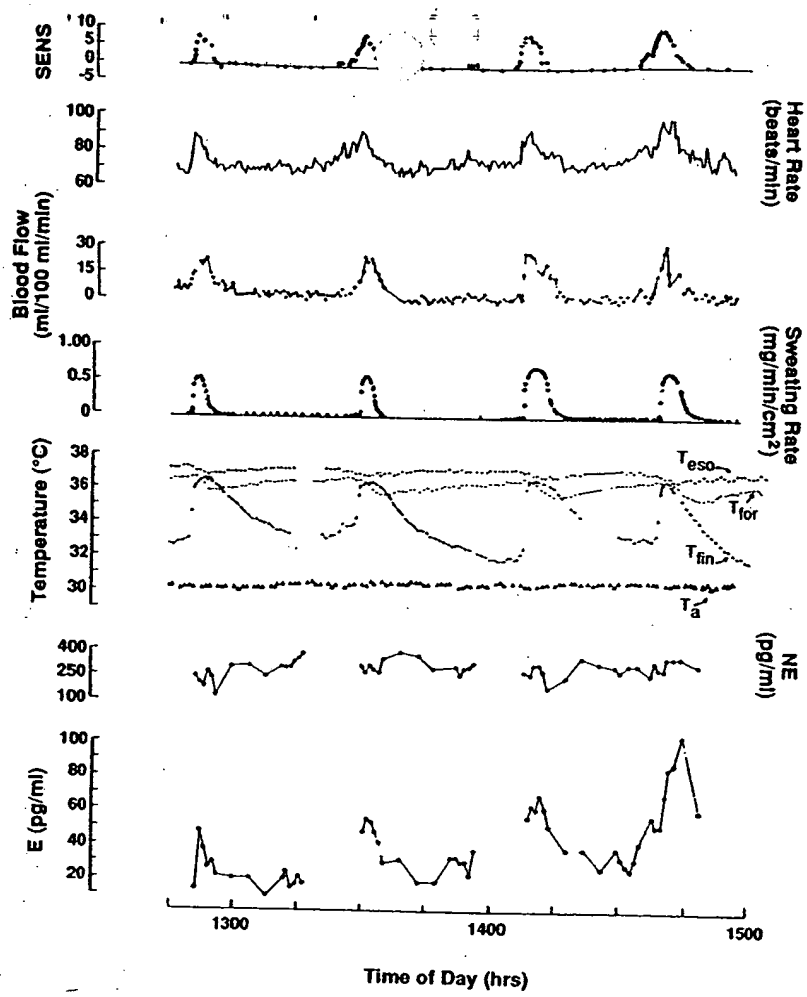

FIG. 7. Pattern of cardiovascular, thermoregulatory, and endocrine changes for four consecutive hot flashes over a 2-hr period. Changes in sensation (SENS), heart rate, blood flow (finger), sweating rate, temperatures (esophageal, forehead, finger, and ambient), norepinephrine (NE), and epinephrine (E) are depicted. (From ref. 85, with permission.)

TABLE 2. *Hormone changes during hot flashes*

Substance	Response	Reference
LH	Increase	35,38,39,46,68,69,120,121
FSH	No change	39,46,68,120
	Increase	38,69
GnRH	Increase	65
Estradiol	No change	46
Estrone	No change	46
Dehydroepiandrosterone	Increase	46
Androstenedione	Increase	46
Progesterone	Slight increase	46
Epinephrine	Increase	35,68
	No change	38,121
Norepinephrine	No change	38,68,120
	Decrease	35
	Increase	121
Dopamine	No change	38,121
Prolactin	No change	38,46,120
Cortisol	Increase	46,69,121
	No change	122
ACTH	Increase	46,69
β-Endorphin	Increase	46,69
β-Lipotropin	Increase	69
Neurotensin	Increase	123
Growth hormone	Increase	46
TSH	No change	46
Glucose	No change	121
Glucagon	No change	121
Insulin	No change	121

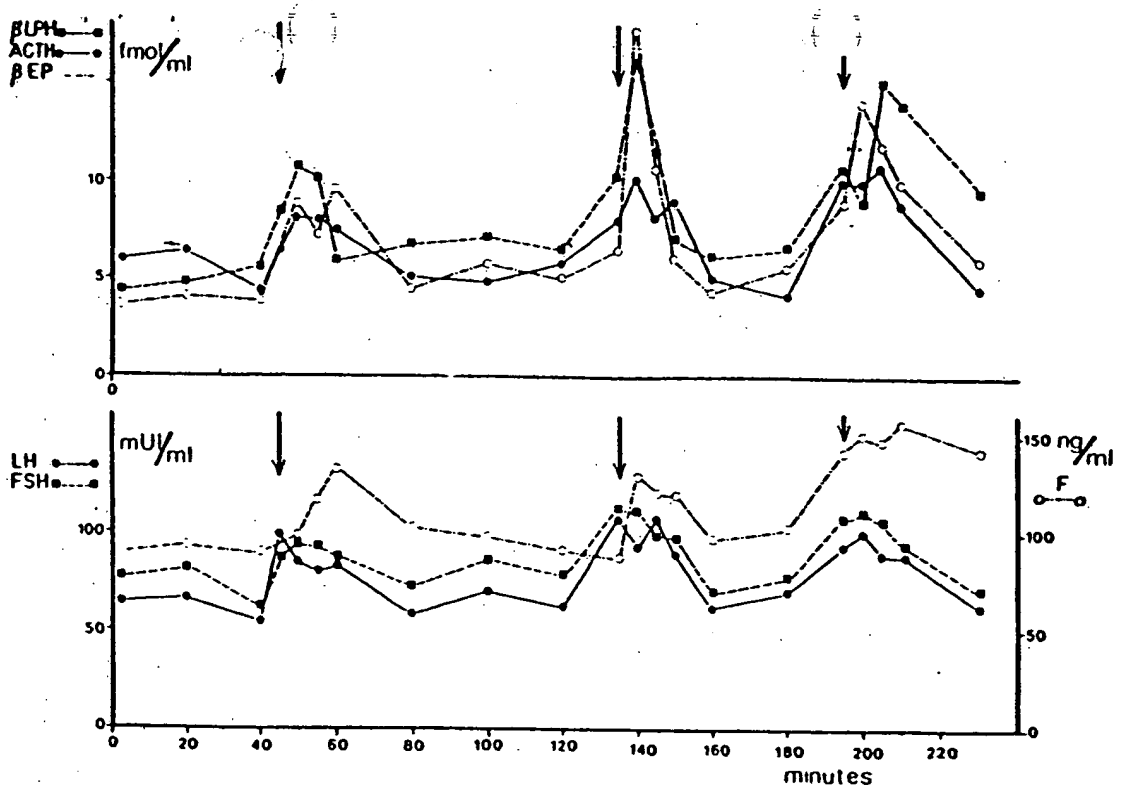

FIG. 8. Plasma levels of adrenocorticotropin (ACTH), β-lipoprotein (β-LPH), β-endorphin (β-EP) (top) and luteinizing hormone (LH), follicle-stimulating hormone (FSH), and cortisol (F) (bottom) in subject M.M. during observation period. *Arrows* indicate onset of hot flashes. (From ref. 69, with permission.)

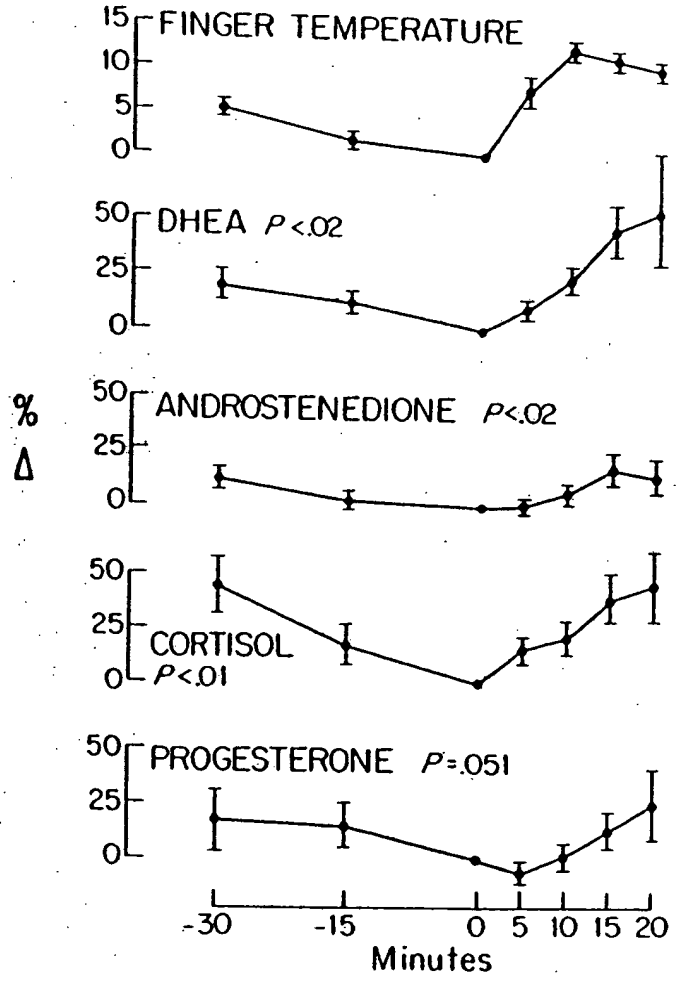

FIG. 9. Mean percent change of finger temperature and serum DHEA, Δ, F, and P levels before and after objective flashes. (From ref. 46, with permission.)

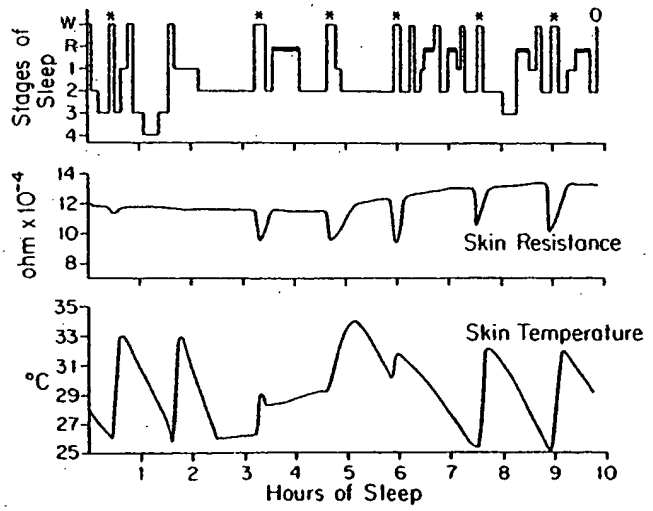

FIG. 10. Sleepgram and recordings of skin resistance and temperature in postmenopausal subject with severe hot flushes. Each *asterisk* marks occurrence of objectively measured hot flush. *Open circle* indicates arousal of patient by investigator at end of the study. (From ref. 71, with permission.)

of hot flashes are reduced with estrogen treatment (Fig. 11) (71,73,74). Sometimes, a woman may not consciously awaken from sleep (even though the EEG recording indicates momentary arousal), yet objective physiological measurement has documented the continuation of hot flashes throughout the night (Fig. 12). This sleep disturbance due to hot flashes is a primary motivator for women to seek medical advice and pharmacologic solutions. As is indicated later, a nonpharmacologic approach may also provide nighttime relief for some women.

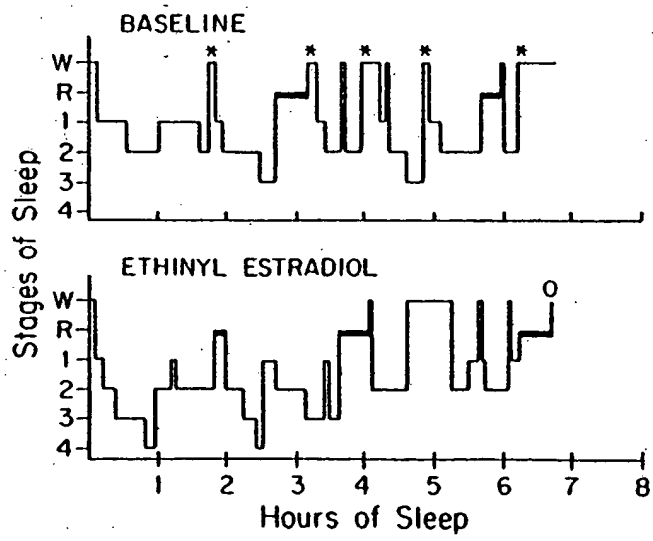

FIG. 11. Sleepgrams measured in symptomatic patient before and after 30 days' administration of ethinyl estradiol, 50 μg four times daily. (From ref. 71, with permission.)

AMBIENT TEMPERATURE AND HOT FLASHES

Many women find that their hot flashes are worse in warm weather. To relieve the discomfort of hot flashes, women may stand in front of an air conditioner or refrigerator, wear loose, light, nonsynthetic clothing, or, on cool nights, open windows. Yet scant research exists on the effect of ambient temperature on hot flashes. Hot flash frequency has been found by some investigators to correlate positively with outdoor temperature (75,76), while others found no relationship to exist (29,30). However, what has long been reported anecdotally, and in some uncontrolled thermal environments, has now been demonstrated under controlled temperature conditions. That is, ambient temperature does significantly influence both the frequency and intensity of hot flashes. In a cool environment (19°C) women had significantly fewer and less intense hot flashes than in a warm (31°C) environment (77) (Fig. 13). Cooling room temperature may therefore be one way in which women can reduce their hot flashes, particularly during sleep.

ETIOLOGY

Several hypotheses to explain the mechanism underlying hot flashes have been put forth (66,78–81). These hypotheses are based on data obtained primarily from studies of women with hot flashes in which substances measured in the peripheral circulation have been found to change in association with the hot flashes, or from observations on the success of various drugs in treating hot flashes. The hypotheses discussed most widely involve α-adrenergic mechanisms, endogenous opioid peptide, and GnRH. There have been a number of detailed reviews and critiques of the proposed models and theories to explain hot flashes (78,79,82–84). The definitive explanation still eludes us.

The hormonal milieu is obviously relevant to the occurrence of hot flashes. However, measuring the endocrine concomitants of hot flashes either in terms of mean hormone levels or episodic changes has not uncovered the initiating factor responsible for triggering a hot flash.

The sequence of events that characterizes a hot flash appears to be the result of a perturbation of the brain's thermoregulatory center located in the hypothalamus, activating mechanisms of heat loss (vasodilation, sweating, and behavioral adjustments) at hot flash onset, and heat conservation (vasoconstriction, behavioral changes, and shivering) at the termination. The combination and sequence of physiological and behavioral responses during a hot flash suggest that the phenomenon involves the coordinated action of the thermoregulatory system. The body responds as it

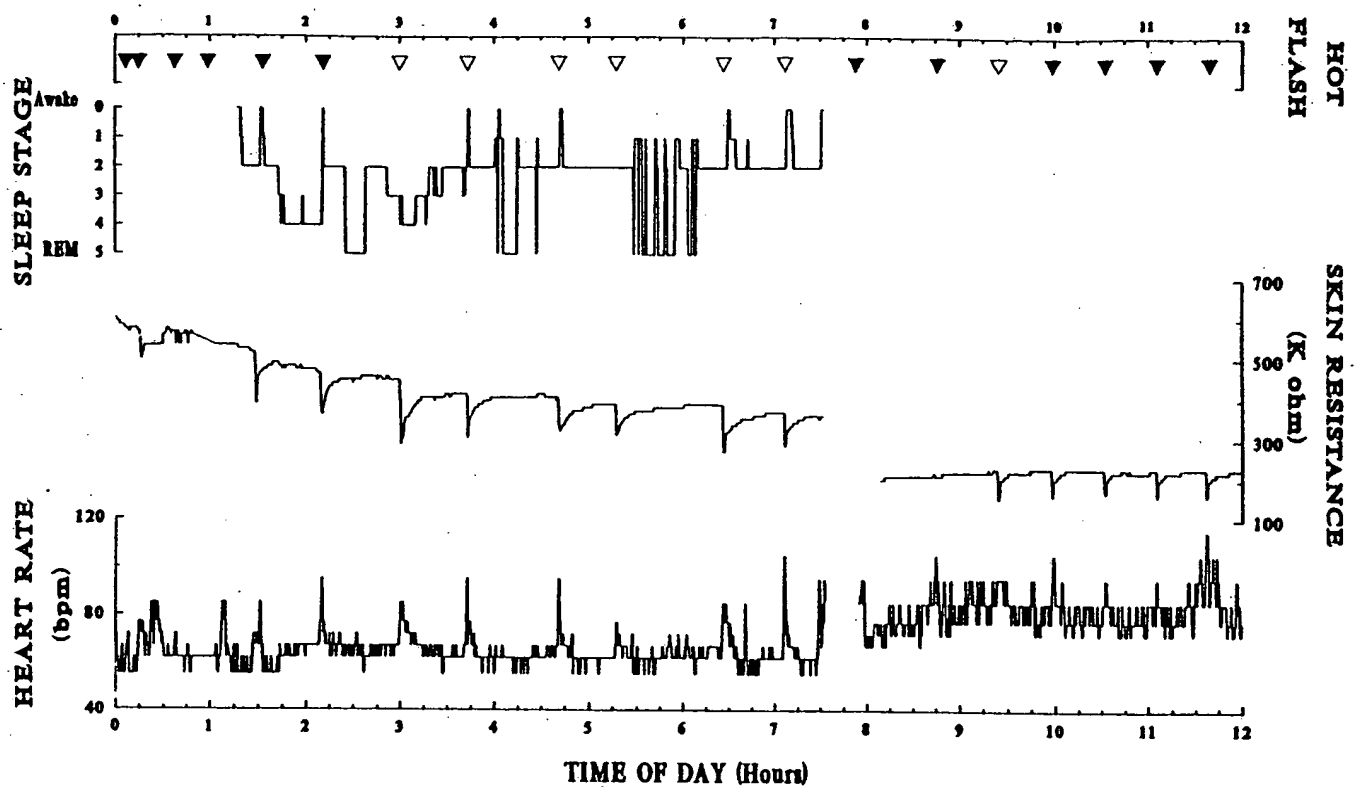

FIG. 12. Pattern of sleep stages, skin resistance, and heart rate for a 12-hr period (subject #A-10). The *solid triangles* (▼) indicate reported hot flashes; *open triangles* (▽) indicate unreported hot flashes. Sleep stages 1 through 4, NREM sleep; stage 5, REM (rapid eye movement); absolute clock time on the *abscissa*. The sudden drop in skin resistance at about 7:00 a.m. is due to a change of skin resistance electrodes. This subject went to bed shortly after 1:00 a.m. and awoke at about 7:30 a.m. (From ref. 14, with permission.)

would to dissipate excess heat in situations of overheating or at the breaking of a fever. Since there is no elevation of internal temperature associated with a hot flash, however, the responses are consistent with the hypothesis that a hot flash involves a transient downward resetting of the body's thermoregulatory set-point (36,85). In other words, at the start of a hot flash there is a sudden drop in set-point temperature. Since the body would then be warmer than this new set-point, the thermoregulatory system acts appropriately to cool the body. As a result, internal temperature falls. The set-point then returns to normal, and heat conservation mechanisms act to return body temperature to normal. This entire process is analogous to what happens during a fever, but the change in set-point is in the opposite direction than during fever (36,85). Pyrogenic substances can raise the set-point temperature and initiate the thermoregulatory responses that result in a fever (86). What remains unknown is precisely what causes the hypothalamic resetting during a hot flash.

Possible candidates include endocrine and neuroendocrinological substances. Reproductive hormones modulate the functioning of the thermoregulatory sys-

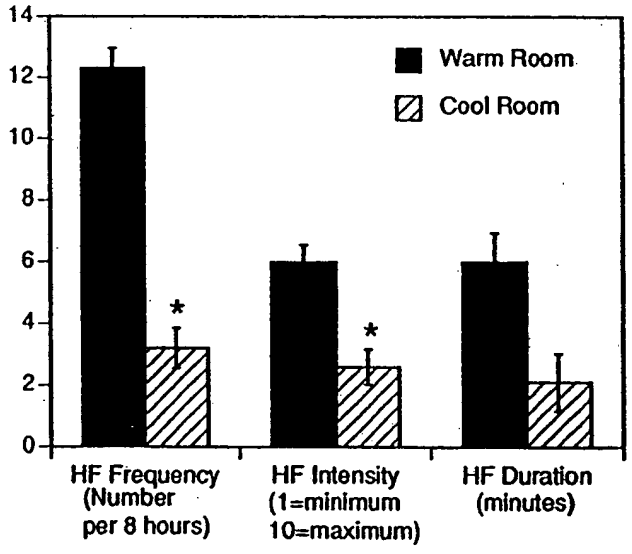

FIG. 13. Mean frequency, intensity, and duration of hot flashes at warm (31°C) versus cool (19°C) ambient temperatures ± 1 SEM. *$p < 0.05$. The units of the *y*-axis vary with parameter, as indicated. (From ref. 77, with permission.)

tem (85), as do opioid peptides (87–89), which also modulate and are influenced by reproductive hormones (90–92). Further delineation of the relationship between sex steroids, opioid peptides, and thermoregulatory function is necessary.

A coherent hypothesis should be able to accommodate the hot flash-associated thermoregulatory and neuroendocrine responses, and be able to explain among other things: (a) why different individuals experience hot flashes at different frequencies and for varying lengths of time, and why some women never get hot flashes; (b) why hot flashes begin in some women just hours after ovariectomy; (c) why some women sweat while others do not; (d) why priming with estrogen is necessary before hot flashes can occur (no hot flashes are seen in prepubertal girls, or women with gonadal dysgenesis before treatment with estrogen); (e) the similar phenomenon of hot flashes in women and men following a reduction in estrogen in women or testosterone in men; (f) the observations that drugs such as clonidine have been demonstrated to eliminate the sensation of hot flashes, while pulses of finger temperature and LH remain. Are there invariant components of a hot flash that are always measurable, independent of environmental conditions, age, or sex? A resolution of these questions awaits additional research, and perhaps an animal model that more closely resembles the human female in terms of both endocrine and thermoregulatory functioning.

WHY ARE HOT FLASHES A PROBLEM?

If hot flashes occur only sporadically, they are not likely to be disruptive or even much greater than a nuisance. But for those women with many hot flashes throughout the day, every day, hot flashes can be periodically disabling, physically draining, and can impact negatively on work, family, and social relationships. When hot flashes disturb sleep every night, the consequences can be debilitating. Some women choose to avoid touching, hugging, or sexual activity because the skin-to-skin contact may bring on a hot flash.

Profuse sweating during a hot flash is one of the most bothersome complaints; it can be an embarrassment, particularly at work or in social situations. It may even require a change of clothing, which is not always possible or convenient. Women with severe hot flashes describe their lives as a constant struggle to achieve thermal comfort. They must adjust their behavior (such as wearing layers of clothes for easy removal, shunning synthetics for natural fibers, or carrying a fan), or they attempt to alter their immediate environment by turning on the air conditioner, opening windows, going outside if the weather is cool, or staying inside on hot humid days.

DIAGNOSIS

Most women who present with hot flashes will be perimenopausal or recently postmenopausal. Therefore age and menstrual history (menstrual cycle irregularity, oligomenorrhea or amenorrhea) give strong indications that these are menopausally related hot flashes, as do other complaints suggestive of low estrogen, such as vaginal dryness and its sequelae. During the perimenopausal period, hot flashes may come and go. Menstrual cycle irregularity may correspond with these fluctuating episodes. If women are still menstruating regularly when hot flashes first occur, they may not recognize that the episodes of feeling hot and sweating are actually hot flashes. Thus there may be many years of hot flashes prior to menopause. And hot flashes may continue long into the postmenopausal years, and sometimes throughout a woman's lifetime.

In the few cases where diagnosis of hot flashes is unclear, it may be of value to measure plasma follicle-stimulating hormone (FSH) and LH, since they are both elevated in menopausal women. However, particularly during the perimenopause, levels of these hormones fluctuate. So multiple measurements would have to be made. FSH is better diagnostically than LH since the increase in circulating LH tends to lag behind the rise in FSH. Estradiol is not a particularly good indicator on which to base diagnosis in women of pre- and perimenopausal ages.

Several conditions share some clinical features with hot flashes, particularly the flushing and sweating. These include hyperthyroidism, panic attacks, carcinoid syndrome, pheochromocytoma, and niacin flush.

MANAGEMENT

Many women can make adjustments necessary to cope with their hot flashes if they are provided with adequate information and support. Women can experience a wide range of sensations during hot flashes. This may be upsetting if they are unaware of what to expect. Many of the worries of women with hot flashes can be allayed if they are informed of what is and what is not known. They could be told, for example, that no one can predict exactly how long their hot flashes will last or, therefore, the necessary duration of treatment. It is also important to convey that hot flashes may recur when treatment is ended.

The initial stages of management should include a determination of the level of impact of the hot flashes and an assessment of how the woman has been coping with them. Precipitating factors such as hot drinks, alcohol, caffeine, or hot environments should be identified and avoided. Stresses at home or in the workplace may also make hot flashes even more difficult to cope with.

Many women try to control their hot flashes by modifying their environment or behavior before consulting a physician. They change room temperature, wear light, layered clothing, and try vitamins or dietary changes that have been suggested to them. For some, these attempts may be effective and the hot flashes may become less intense or less frequent. While for others, nothing they do has any impact on their relentless hot flashes. When knowledge, proscription, and behavioral changes prove insufficient, women may ask about hormone therapy.

Pharmacologic Preparations

The available therapies do not "cure" hot flashes; rather, they provide symptomatic relief by making the hot flashes less frequent and/or less intense, or sometimes by eliminating them, at least for the duration of the treatment. If hot flashes return when treatment is stopped, it is not known whether the treatment just postponed the hot flashes, or whether the individual would have had hot flashes for that duration regardless of whether she had been treated. To minimize the recurrence of hot flashes, it is advisable to taper drug treatment over several weeks, rather than stopping suddenly. We do not know the mechanism by which hot flashes are reduced for any of the treatments discussed below.

When various hot flash therapies are compared with a placebo, the placebo often demonstrates considerable effectiveness. Therefore to best assess the efficacy of a treatment, it is necessary to conduct randomized, double-blind, placebo-controlled crossover studies. And, as it may take several weeks to effectively control hot flashes, studies must be of sufficient duration to adequately determine how well a particular treatment works.

Estrogen

Estrogen administration is currently the most effective treatment for hot flashes. It has been used, albeit initially in the form of crude extracts, for almost 100 years. The rationale is based on the association of hot flashes with the decline in ovarian function at menopause rather than on the knowledge of the cause of hot flashes.

The effect of estrogen treatment on hot flashes is not usually immediate. The full benefit may not be realized until several months of therapy. When treatment is discontinued, the effect on hot flashes may persist for some time, depending on the type of estrogen or route of administration. For example, conjugated equine estrogen may remain active for several weeks after treatment has ended, due to storage in adipose tissue (93). Many patients on a cyclic estrogen regimen may find that, for each cycle, it takes several days before hot flashes diminish, and by the end of the week in which no estrogen is taken, hot flashes have returned. For this and other reasons, the current trend is toward prescribing continuous daily estrogen.

The most commonly used regimen for treating hot flashes in the United States is 0.625 to 1.25 mg of oral conjugated equine estrogen (Premarin). Many other oral preparations are available in equivalent doses (see Chapter 6). Transdermal estradiol (Estraderm 0.05 to 0.10 mg/day) has been gaining popularity. Estrogen is also available as subcutaneous implants, injectables, and vaginal creams. Most are effective in treating hot flashes.

Oral estrogen has been in use for many years and has been the most extensively studied of the treatments for hot flashes. In a double-blind, placebo-controlled crossover study of conjugated equine estrogen (1.25 mg), Coope et al. (94) reported that after the first 3 months, hot flashes were reduced by about 90% in women on estrogen and by about 62% in women on placebo (Fig. 14). In another placebo-controlled trial, Campbell and Whitehead (95) sought to assess the efficacy of conjugated estrogen (1.25 mg) in relieving hot

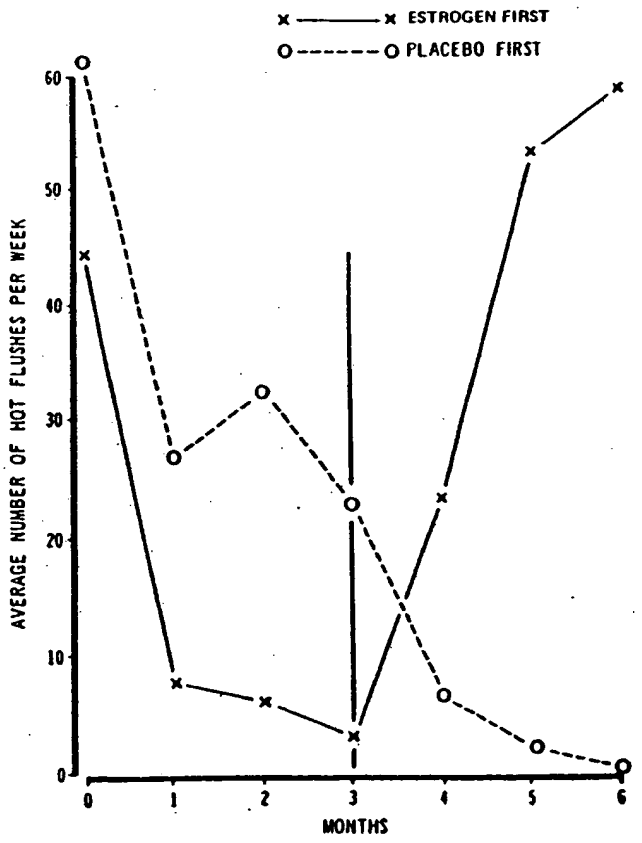

FIG. 14. Hot flush count during the 6-month trial. (From ref. 94, with permission.)

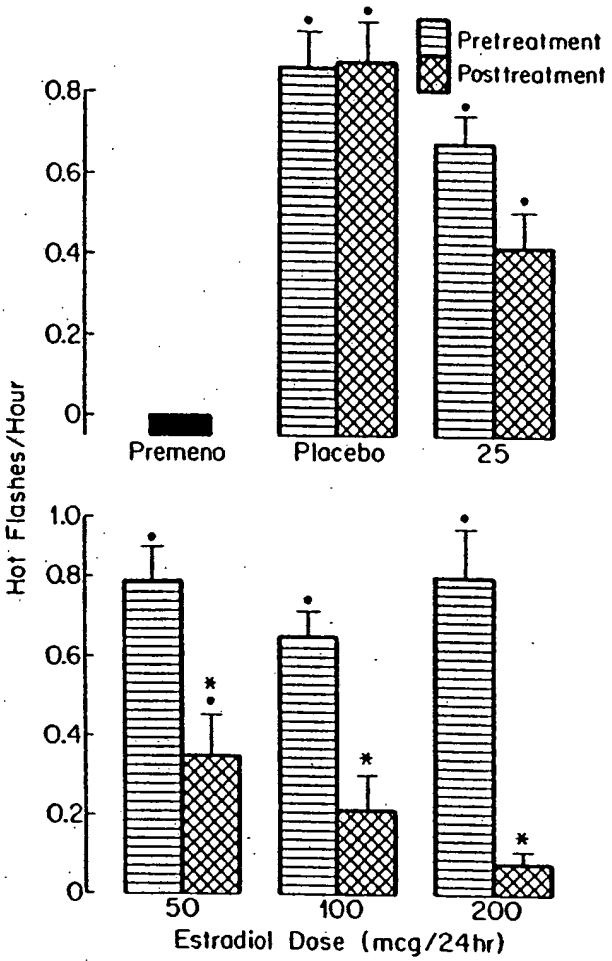

FIG. 15. Mean ± SE rate of occurrence of hot flashes in the study groups and premenopausal women (Premeno) before and during transdermal E_2 administration. (From ref. 96, with permission.)

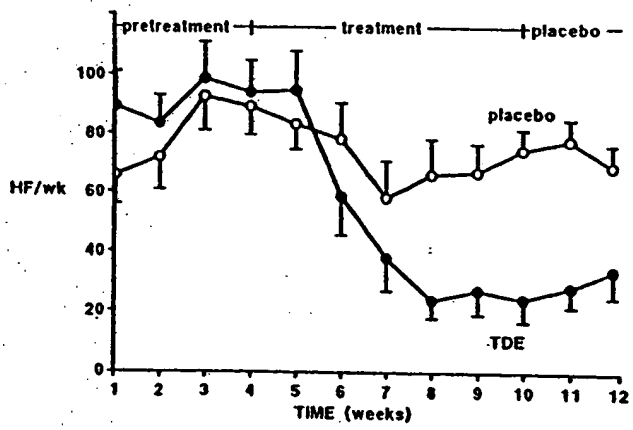

FIG. 16. Total subjective hot flashes (HF) recorded by patients on transdermal estradiol (TDE) patch (N = 10) and placebo (N = 8, first seven weeks; N = 7, last five weeks) for each study week. (From ref. 97, with permission.)

flashes and other symptoms of menopause such as vaginal dryness, insomnia, anxiety, irritability, and memory loss. Estrogen was significantly better than placebo in improving all these symptoms. Hot flashes were improved by 40% to 50% with estrogen and by approximately 10% with placebo (as assessed by graphic rating scores). In this study, one group of subjects had symptoms such as insomnia, but they did not have hot flashes. Treatment with estrogen improved some of their symptoms, but not their insomnia. This is in contrast to the alleviation of the insomnia for those women who also complained of hot flashes. The investigators concluded that much of the insomnia of women with hot flashes is the result of nocturnal hot flashes.

Transdermal patches provide a continuous diffusion of estradiol and are effective in reducing hot flashes. A dose–response relationship between dose of transdermal estradiol (25, 50, 100, and 200 μg/24 hr) and hot flash frequency, using subjective and objective criteria, was demonstrated in a double-blind study by Steingold (96) (Fig. 15). Hot flashes were significantly reduced at all doses of estradiol, with a progressive decline in hot flashes as estradiol increased; hot flashes were not appreciably reduced by placebo. The highest dose of 200 μg/day resulted in a 91% reduction in the number of hot flashes.

Haas et al. (97) compared the effects of 6 weeks of transdermal estradiol (10 cm^2, 50 μg/day) with that of placebo, on subjectively and objectively measured hot flashes in a double-blind, placebo-controlled study. While changes in plasma estradiol and LH levels were measurable within 8 hr of the application of the patch, a decline in hot flashes occurred only gradually over the next 4 weeks. At that point there was a 74% decrease in subjectively reported hot flashes and an 85% decrease in objectively monitored hot flashes (Fig. 16). Women on placebo reported a 27% reduction in hot flashes (not statistically significant) during the first 3 weeks of the study.

Stanczyk (98) compared transdermal estradiol with subdermal estradiol. Hot flashes were eliminated in all patients, regardless of the mode of estrogen delivery.

In addition to ameliorating hot flashes, other complaints that may be improved by estrogen include insomnia (74,95), vaginal dryness (95), memory/concentration (95), lower urinary tract problems (95), and mood (95,99).

Nonestrogenic Treatments

Although most women find that estrogen relieves their hot flashes, there are some for whom estrogen is contraindicated or who find the side effects unacceptable, some whose hot flashes are not responsive to es-

trogen, even at elevated doses, and others who prefer not to remain on estrogen for a prolonged period of time.

Progestins

Medroxyprogesterone acetate (MPA) is a nonestrogenic steroid. Several double-blind, placebo-controlled studies have shown that MPA decreases the number of hot flashes. Injected intramuscularly, a dose of 150 mg/month MPA resulted in a 90% reduction in hot flashes, compared with a 25% reduction in the placebo group (100). The major side effect was abnormal uterine bleeding (43%). Morrison et al. (101) conducted a study of MPA (50, 100, and 150 mg im) in which a dose–response relationship was shown, with about 75% improvement for those on 50 mg, and 90% to 100% relief for those on 150 mg by week four of treatment. Most women in the placebo group dropped out of the study. For those who remained, the placebo was ineffective. In this study, only two subjects on MPA (of 36 women) had abnormal bleeding.

Taken orally, MPA has fewer side effects. In a double-blind, placebo-controlled trial, MPA (20 mg/day) resulted in an approximately 74% decline in the number of reported hot flashes by the third month of treatment; placebo caused a reduction in hot flashes of about 26% (Fig. 17) (102). Albrecht et al. (103) measured hot flashes both subjectively and objectively in response to 20 mg/day, oral MPA. Reported hot flashes decreased by 90% in women on MPA and by 25% in those on placebo. Finger skin temperature elevations and associated LH pulses, the objective indicators of hot flashes, were also reduced.

Another progestin, megestrol acetate (MA), has been tested and found to be effective in treating hot flashes. Oral MA significantly reduced hot flashes (no placebo control) whether measured subjectively or objectively, in a dose–response fashion with increasing doses of MA (20, 40, 80 mg/day) (Fig. 18). Few side effects were reported, and no abnormal bleeding or depression (124).

Sherwin and Gelfand (104) compared women on conjugated equine estradiol alone, with those on estradiol + medroxyprogesterone acetate (MPA). Both regimens resulted in a reduction in hot flashes. Estradiol was administered on days 1 to 25, and MPA on days 15 to 25, leaving days 26 to 30 hormone-free. For 3 weeks of each cycle hot flashes were diminished. During the fourth week, which was hormone-free, hot flash frequency increased.

Clonidine

Clonidine, an α-adrenergic receptor agonist that influences vascular responsiveness, has been used in the treatment of hot flashes. Clayden and colleagues (105) reported a double-blind, placebo-controlled crossover study of 86 women with hot flashes, and they demonstrated that clonidine (0.05 to 0.15 mg/day) reduced the

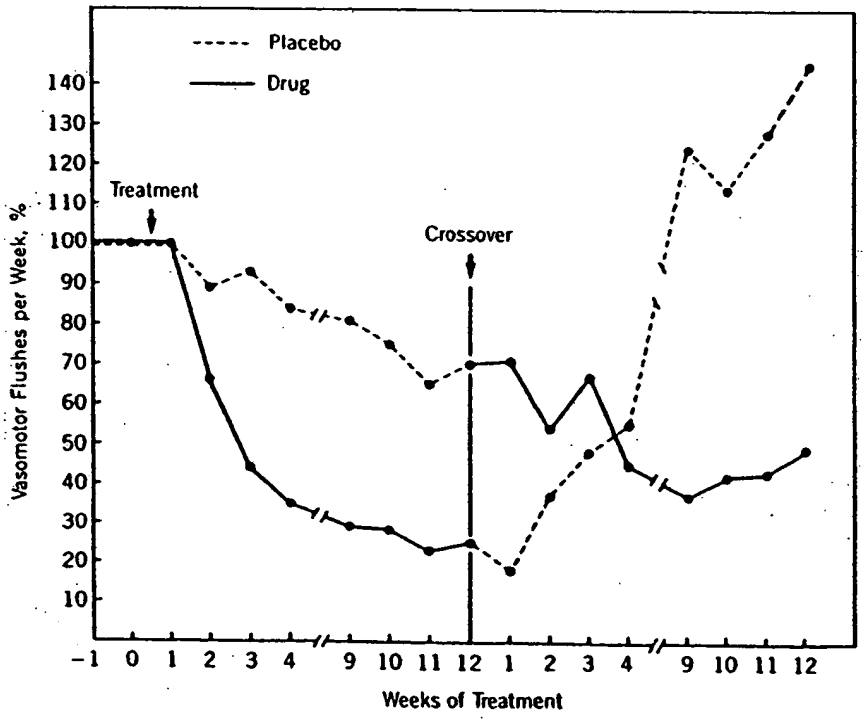

FIG. 17. Effect of oral medroxyprogesterone acetate on frequency of hot flashes. Mean number of vasomotor flushes as a percent change from pretreatment (week −1 to 0). (From ref. 102, with permission.)

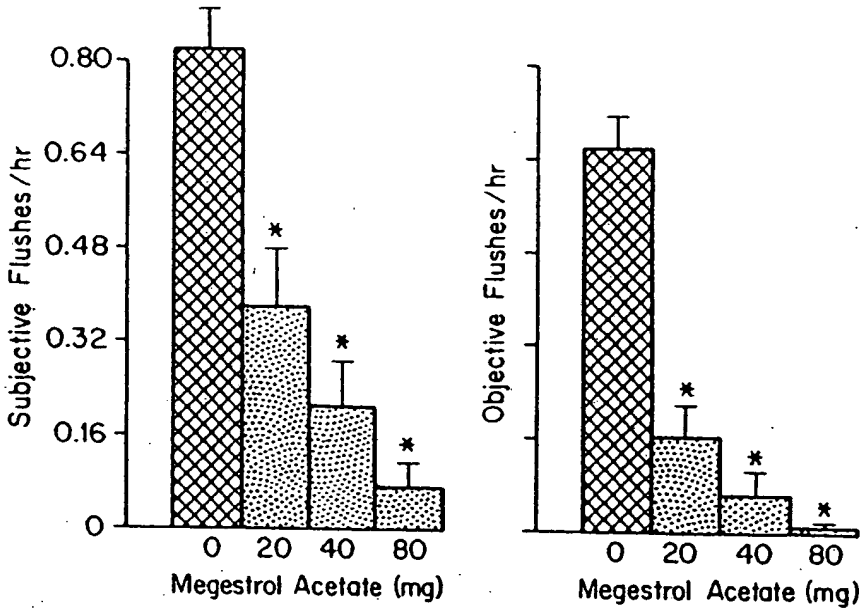

FIG. 18. The mean (±SE) subjective and objective flushes per hour before and following the oral administration of the various doses of megestrol acetate. *Significantly different ($p < 0.01$) from baseline. (From ref. 124, with permission.)

number and intensity of hot flashes. However, as in the studies of estrogen, women on placebo also reported a reduction in hot flashes almost equal to that of women on clonidine (Fig. 19). Dry mouth was the primary complaint of those on clonidine. Other side effects, including insomnia, headache, depression, and nausea, were reported both by those on clonidine and on placebo. In another study, Laufer and co-workers (106) demonstrated a dose–response relationship between clonidine (0.1, 0.2, 0.4 mg/day) and objectively recorded hot flashes in six women. At the highest dose, reduction in hot flashes was 46%; the reduction with placebo was small and not statistically significant. Of the initial 10 subjects, four withdrew due to side effects, which included nausea, fatigue, headaches, dizziness, and dry mouth.

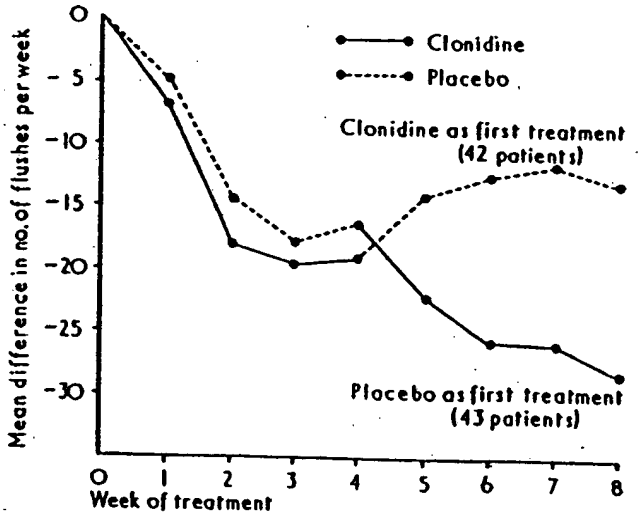

FIG. 19. Mean change in number of flushes from initial values. (From ref. 105, with permission.)

When clonidine was administered intravenously to menopausal women with hot flashes, Tulandi et al. (107) obtained somewhat different results. Subjects who received clonidine (0.075 mg in 10 ml physiological saline) did report significantly fewer hot flashes; however, objective recordings indicated a continuation of the pattern of episodic increases in finger skin temperature and the associated pulses of LH characteristic of hot flashes.

Ginsburg et al. (108) examined vascular responsiveness in menopausal women before and after oral clonidine treatment. They measured peripheral vasodilatory responses to infusion of the vasoactive substances norepinephrine, epinephrine, and angiotensin. Forearm and hand blood flow responses in the infusions were diminished after clonidine treatment. The investigators suggest that clonidine might reduce the peripheral vasodilation that accompanies a hot flash, and that given the reduced response to angiotensin, clonidine might be acting in some way other than through peripheral adrenergic mechanisms.

Lofexidine, another alpha-agonist, and α-methyldopa, whose primary metabolite, α-methylnorepinephrine, is an α-receptor agonist, have also demonstrated effectiveness in reducing hot flashes (109,110).

Propranolol

Propranolol, a peripherally and centrally acting beta-receptor blocking agent, has been studied with

mixed results. Erkkola and colleagues (111) reported that 60 mg/day of propranolol slightly reduced hot flashes. The reduction was from approximately 9.4 hot flashes/day to 7.8 hot flashes/day. There was no placebo control. Coope et al. (75), in a randomized double-blind placebo-controlled trial, found 40 mg of propranolol daily to be no more effective than placebo in reducing hot flashes. The slight reduction in hot flashes was similar to that reported by Erkkola. No side effects were seen among the women on propranolol. A statistically significant reduction in hot flash frequency was reported by Alcoff et al. (112) in 70% of their subjects. However, there was no report of the extent of the reduction, so it is difficult to assess whether this had clinical significance. Side effects (including lightheadedness, nausea, and fatigue) occurred in 24% of those on propranolol (80 mg/day).

Bellergal

Bellergal is a combination of belladonna alkaloids, ergotamine tartrate, and phenobarbital. In a double-blind, placebo-controlled study, Lebherz and French (113) found Bellergal to be significantly more effective than placebo are reducing subjectively reported hot flashes (60% decrease in hot flashes versus 22% decrease, respectively). The specific mechanism of action on hot flashes is unknown. Bellergal has sedative effects and is not a treatment of choice. One must also consider the varied actions of the three components and be aware of possible interactions with other drugs.

NONPHARMACOLOGIC APPROACHES

The impetus to explore alternative therapies springs not from a pressing need for a more effective treatment, since estrogen is very effective, but primarily from a concern over the safety of estrogen treatment, and a need for alternatives for those for whom estrogen is contraindicated, who cannot tolerate estrogen, or who choose not to take estrogen. Unfortunately, the therapeutic efficacy of most alternatives has not been adequately tested.

Ambient Temperature

As indicated earlier, the surrounding air temperature can have a significant impact on both the frequency and intensity of hot flashes. For women who have difficulty sleeping due to frequent hot flashes, maintaining a cool bedroom temperature is one way to ameliorate hot flashes and reduce nighttime awakenings. It is not as easy to control the temperature of one's environment during the day, but if possible to achieve, a cool environment would reduce hot flashes.

Vitamin E

In the 1940s a number of studies tested the effectiveness of vitamin E in treating hot flashes (114–116). Most of these investigations found vitamin E to have value in treating hot flashes. But the studies were neither double-blind nor placebo-controlled. In 1953, Blatt et al. (117) conducted a double-blind study comparing the effect of vitamin E, estrogen, and a placebo (no crossover) on a complex of menopausal symptoms (not hot flashes alone, but as part of a group of 11 symptoms). They found vitamin E to be no more effective than placebo, and considerably less effective than estrogen in treating this symptom complex. This study is often quoted as demonstrating the lack of effectiveness of vitamin E for treating hot flashes, a conclusion that cannot be drawn from the data. Some women report anecdotally that vitamin E is very effective in ameliorating their hot flashes (F. Kronenberg, *unpublished data*). A properly controlled study of vitamin E and hot flashes is warranted in order to determine the degree of effectiveness and for whom the treatment might be most effective.

BEHAVIORAL TREATMENTS

Behavioral methods for moderating hot flashes have received limited study. Freedman and Woodward (81) compared paced respiration and muscle relaxation for their effects on objectively recorded hot flashes. Paced respiration training significantly reduced the frequency of hot flashes (by about 40%) as compared with progressive muscle relaxation training. A variety of behavioral modalities should be evaluated in rigorously designed studies.

Acupuncture

Studies to evaluate the effectiveness of acupuncture in treating hot flashes are underway. Preliminary data from Hammar and colleagues (118) suggest that electrostimulated acupuncture decreases the frequency of hot flashes. Data are as yet insufficient to make possible conclusions or recommendations.

Exercise

The effect of exercise on hot flashes is being investigated. Hammar et al. (119) found that women who belonged to a "gymnastic club" reported less severe

hot flashes than women who did not belong. They did not, however, investigate the physical activity of the latter group. Since exercise results in a great variety of physiological changes, a more rigorous study is needed to determine what component of exercise-induced responses might be responsible for the amelioration of hot flashes.

Diet

Information on how specific foods affect hot flashes is anecdotal. Some women report that caffeine, alcohol, or spicy foods seem to trigger hot flashes. Eliminating foods suspected of aggravating hot flashes can be tried. No scientific data are available regarding either short-term trigger effects or longer-term effects of dietary patterns on hot flashes.

CONCLUSION

We have gained considerable knowledge about hot flashes over the past two decades, although many questions remain unanswered and the specific genesis of hot flashes remains unknown. Even the role of estrogen in the etiology of hot flashes, or the mechanism by which estrogen relieves hot flashes, is still not understood.

While the patterns of hot flashes may be varied, there are commonalities in their physiology and subjective manifestations. Yet the significance of hot flashes to an individual woman's quality of life varies greatly. Currently in the United States there are about 40 million women of menopausal age. The majority of women will at some time experience hot flashes, and for most of these women, hot flashes will last 1 to 3 years and will not be particularly frequent or disruptive. However, 3 to 5 million women will have severe and frequent hot flashes that can be physically and psychologically debilitating. These are the women who most likely would seek medical assistance.

During a hot flash, elements of thermoregulatory, cardiovascular, and endocrine systems act in concert. These elements simultaneously serve other, nonthermal functions such as keeping blood flow and blood pressure regulated. It is an immense challenge to the researcher, given physiological complexity, to produce an explanation of hot flashes that integrates these various interacting physiological factors, as well as behavioral, psychophysiological, and even psychosocial components. Understanding the cause of hot flashes would provide insights into normal and abnormal changes at menopause. A more complete knowledge of the thermoregulatory, cardiovascular, and psychophysiology of women with hot flashes as compared to women without hot flashes may enable us to predict who is most likely to be affected, and to identify additional approaches to the management and treatment of hot flashes.

As information increases about factors that are predictive of hot flashes, and about other heath problems that can influence treatment choice, an individualized approach is increasingly indicated. One dose, regimen, or approach does not fit all women. This makes it all the more urgent to understand the underlying physiology, so we can broaden the treatment options available to women.

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THE HENRY J. KAISER FAMILY FOUNDATION

Prescription Drug Trends

a chartbook

July 2000

Prescription Drug Trends

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July 2000

Top 20 Prescription Drugs Ranked by Number of Dispensed Prescriptions, 1998

exhibit 3.16

Rank	Product	Indication	1998 Prescriptions Dispensed (Million)	Brand or Generic?	Year First Marketed
1	Premarin (Wyeth-Ayerst)	hormone replacement	46.8	B/G	1964
2	Synthroid (Knoll)	thyroid replacement	38.8	B/G	1963
3	Hydrocodone w/APAP (Watson)	narcotic analgesic	29.4	G	1977
4	Trimox (Apothecon)	antibiotic	28.5	G	1977
5	Prilosec (Astra-Merck)	anti-ulcerant (proton pump inhibitor – PPI)	26.7	B	1989
6	Albuterol (Warrick)	bronchodilator	26.0	G	1982
7	Lipitor (Parke-Davis/Warner Lambert)	cholesterol-lowering	24.9	B	1997
8	Prozac (Dista/Lilly)	SSRI anti-depressant	24.8	B	1987
9	Lanoxin (Allen & Hansbury)	cardiotonic (for heart failure)	24.2	B/G	1967
10	Norvasc (Pfizer)	calcium channel blocker (for hypertension)	23.4	B	1992
11	Claritin (Schering)	antihistamine	22.3	B	1993
12	Zoloft (Roerig/Pfizer)	SSRI anti-depressant	21.0	B	1992
13	Paxil (SmithKline Beecham)	SSRI anti-depressant	19.0	B	1993
14	Vasotec (Merck)	calcium channel blocker (for hypertension)	18.5	B	1986
15	Zocor (Merck)	cholesterol-lowering	18.5	B	1992
16	Prempro (Wyeth-Ayerst)	hormone replacement	18.3	B	1995
17	Coumadin Sodium (DuPont)	anti-coagulant	17.9	B/G	1954
18	Zestril (Zeneca)	ACE inhibitor (for hypertension)	17.5	B	1988
19	Glucophage (Bristol-Myers Squibb)	anti-diabetic agent	17.2	B	1995
20	Augmentin (SmithKline Beecham)	antibiotic	15.7	B/G	1984

notes

B = Brand name (has remaining patent life; no generic versions available).

B/G = Brand name product but generics available.

G = Generic.

Rankings and number of prescriptions represent total prescriptions dispensed through independent, chain, foodstore, long-term care, and mail order pharmacies.

sources

Sonderegger Research Center analysis, based on:

Prescriptions Dispensed from IMS Health, Inc., *National Prescription Audit (NPA) Plus*, published in *Medical Marketing & Media*, May 1999.

Year First Marketed from Top 200 listing published in *Pharmacy Times*, April 1999.